

CHAPTER 4

AMINOLYSIS OF *p*-NITROPHENYL

ACETATE

4.1 Introduction

Enzymes, the agents responsible for bio-catalysis, have been a subject to fascination for scientists throughout the 20th century. Their ability to catalyze biochemical reactions at high rates, in water at neutral pH and room temperature, with high selectivity has posed many questions about their mechanism of action. The question of how enzymes achieve such high rates of catalysis is a fundamental issue which had led chemists on a continuing search for simple models where the rates and selectivity of biological catalyst are mimicked.^{1,2}

In term of discussing the importance of enzyme, we need to focus on the possible reaction that can occur. Proton transfer is the most common enzyme-catalyzed reaction. It is also occurred in acid/base catalysis.³ Acid-base reactions are the most common reactions in chemistry and catalysis by acids and bases is extremely common in chemical reactions.⁴⁻⁶ Even the complex biochemical catalysts, enzymes, utilize catalysis by acids and bases. These types of reaction can be divided into several parts. Specific acid-base reactions can be classified as the reaction that involve strong acid-strong base which are H^+ and OH^- respectively. Mean while, general acid-general base reactions are involved weak acids and weak bases. The study of inter- and intra-molecular catalysis in chemical reactions has been of great importance in attempts to understand the mechanism of enzyme action because of the striking resemblance proceeding through an enzyme-substrate complex.⁴⁻⁶

Serine proteases, which consist of trypsin, chymotrypsin, and elastase, catalyze the hydrolysis of protein peptide bonds.^{6,7} Although the mechanism of most of the enzyme catalyzed the reaction are unknown, the mechanism of chymotrypsin-catalyzed hydrolysis of peptide bonds has been relatively well understood.⁸ The

“charge – relay” mechanism postulated for the enzymatic cleavage of peptides bond by serine proteases involves IGA – IGB catalysis.⁷⁻¹² Other than IGA- IGB catalysis, efficient rate enhancements in enzymatic reactions are also found that involve proton transfer.¹³ The understanding of the mechanism of enzyme-mediated reaction becomes important in drug design synthesis and in some biological reaction related to biotechnology.^{14,15}

The reaction of carboxylic acid derivatives such as esters, amide, acid halide and anhydride have long been the subject of investigation. The reaction of amines with derivative of carbonyl compounds, also known as aminolysis have been investigated and their reactions mechanisms have been well clarified.¹⁶ One of the reactions of carboxylic acid derivative is the hydrolysis of ester. Ester hydrolysis is an important and prevalent reaction in both organic and biological chemistry.¹⁷ The classical mechanism for the hydrolysis of esters involves stepwise nucleophilic addition and elimination via a tetrahedral intermediate.¹⁸⁻²² However, it has been argued that these reactions may occur via concerted mechanism depending on reaction medium.^{17,23} Besides that, the modification of the electrophilic centre from C=O to C=S and C=O to C= P also attract extensive attention.²⁴⁻²⁸

The mechanism of aminolysis of ester has received extensive attention.¹⁷⁻²³ The cleavage of an ester in the amine buffers might involve either nucleophilic catalysis or GA – GB catalysis by buffer component.²⁸ In some cases, the two mechanisms may occur concurrently.¹⁷ Reactions of esters and imides with amines have generally been understood to proceed through a stepwise mechanism involving zwitterionic tetrahedral intermediate (T^\pm).¹⁷⁻²³ The presence of more than one tetrahedral intermediate has been also reported.¹⁹ The presence of these intermediates

have attracted interest to further such study. GA – GB catalysis of ester hydrolysis is of particular interest from the viewpoint of enzymatic hydrolysis.^{16,29}

4.2 Effects of Amines on the Cleavage of 26

In order to study the effect of amine buffers on the aminolysis of **26**, the reactions were carried out at different concentration of buffers. In order to maintain a constant pH, the amine employed as buffer as well as nucleophile. Ionic strength was maintained constant at 0.4 M or 0.3 M by addition of NaBr. The concentration of substrate was kept constant at 6×10^{-5} M. The rate of aminolysis of **26** at different concentrations were determined by following the increases in absorbance of phenolate ion as a function of reaction time at 400 nm. The temperature of the reaction was kept constant at 30°C. The amine concentration was maintained in large excess over that of ester in order to obtain pseudo-first-order kinetic.

All buffer solutions were freshly prepared shortly before the start of the kinetic run by addition of calculated amount of standardized hydrochloric acid or sodium hydroxide to the known concentration of free amines. The pH values of the kinetic solutions were determined both prior to and after each kinetic experiment.

Because of the solubility problem, all the stock solutions of kinetic mixtures were prepared in mixed solvent containing 50 % v/v CH₃CN : 50 % v/v H₂O except the stock solution of hydrochloride acid and sodium hydroxide which were prepared in 100 % double distilled water. The solvent transfer from H₂O to CH₃CN – H₂O mixtures would influence not only reactivity but also the basicity of the nucleophiles.

4.3 Results

4.3.1 Effect of Primary Amines on the Cleavage of **26**

The organic – aqueous cleavage of **26** was studied in buffer solutions of methylamine (CH_3NH_2) within pH range $9.80 \pm 0.4 - 10.63 \pm 0.05$ and benzylamine ($\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$) within pH range $8.28 \pm 0.07 - 9.31 \pm 0.01$ at 30°C . The values of pseudo-first-order rate constant, k_{obs} , obtained using nonlinear least-squares technique from Eq. (3-13) for every kinetic runs of reaction between **26** with these amines are shown in Tables (A-1 to A-3) in Appendix. The plot of Abs versus time for a typical kinetic run is shown in Fig. 4-1. All the reactions were carried out for the reaction period required for the completion of more than 90 %.

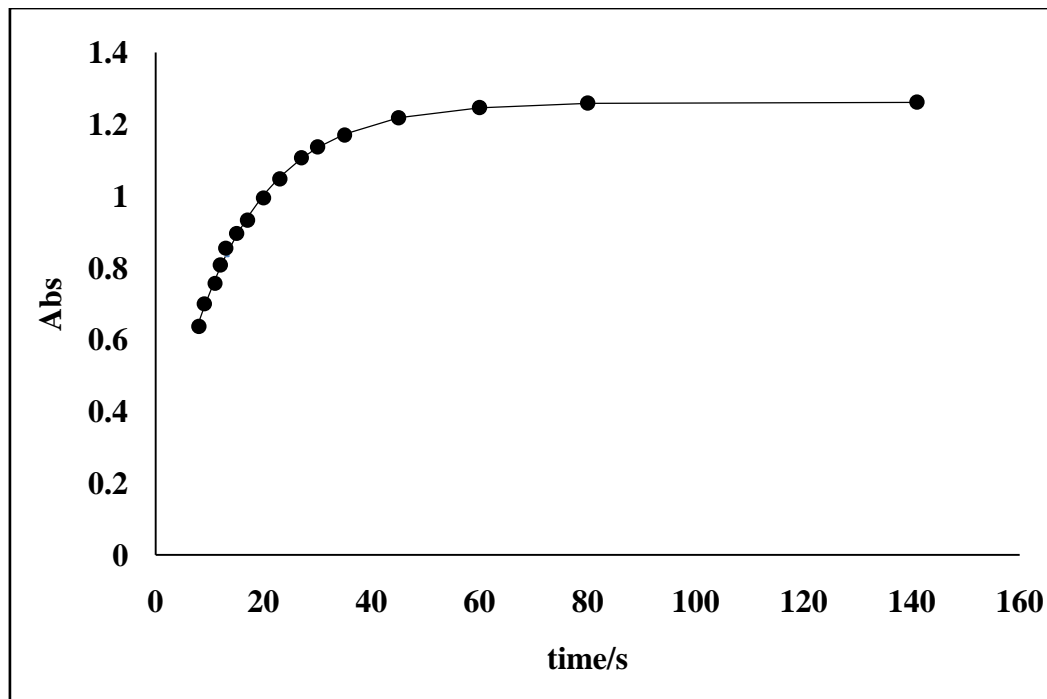


Figure 4-1: Plot of Abs versus time, t , for the aminolysis of 6×10^{-5} M **26** at 0.02 M $[\text{CH}_3\text{NH}_2]_{\text{T}}$, 50 % free base, $\mu = 0.4$ M and $T = 30^\circ\text{C}$. The solid line is drawn through the calculated data points using Eq. (3-13).

The plot of k_{obs} versus total amine buffer concentrations ($[\text{Am}]_{\text{T}}$) at different pH for the aminolysis **26** with **43** and **49** at $\mu = 0.4$ M are shown in Figs. 4-2 and 4-3 respectively. The values of k_{obs} at different $[\text{Am}]_{\text{T}}$ and constant pH were treated with Eq. (3-15). The fitting of the observed data to Eq. (3-15) is evident from the plots of Figs. 4-2 and 4-3. The values of k_{o} , k_{b} and k_{bcald} are summarized in Tables 4-1 and 4-2.

The plot of k_{obs} versus total amine buffer concentration ($[\text{Am}]_{\text{T}}$) at different pH for the aminolysis **26** with **43** at $\mu = 0.3$ M are shown in Fig. 4-4. The fitting of the observed data to Eq. (3-15) is evident from the plots of Fig. 4-4. The values of k_{o} , k_{b} and k_{bcald} are summarized in Tables 4-3.

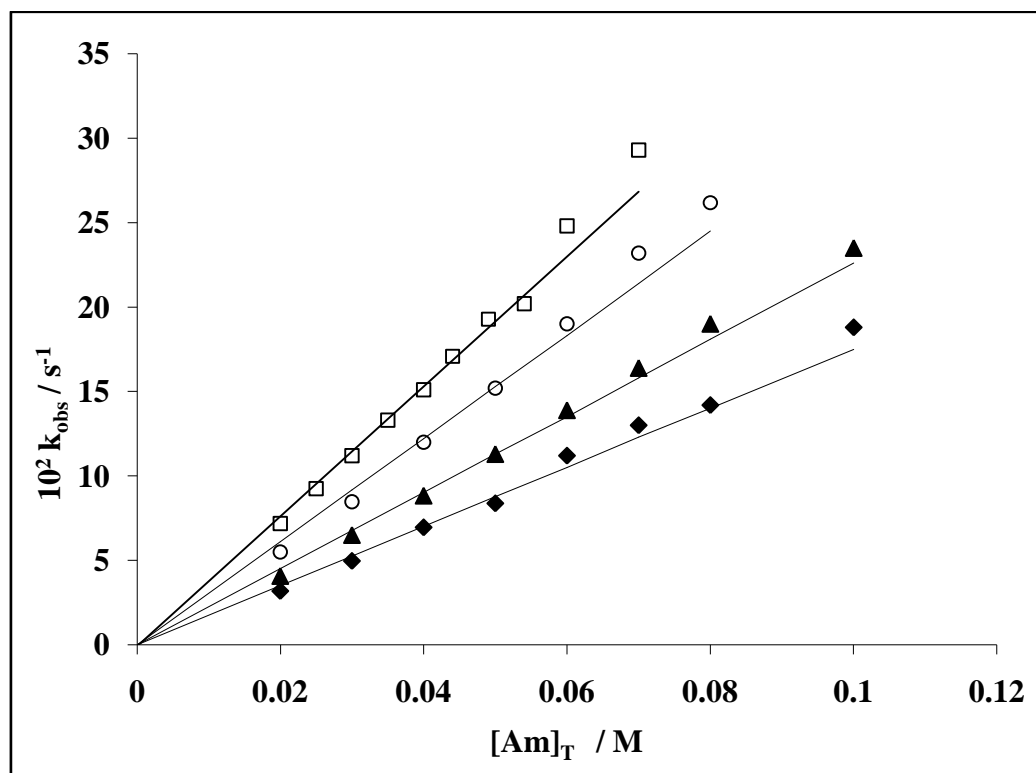


Figure 4-2: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{49}]_{\text{T}}$, $\mu = 0.4$ M at pH 9.80 (\blacksquare), 10.15 (\blacktriangle), 10.35 (\circ), and 10.56 (\square) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-1: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **49** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^3 k_o^b$ (s ⁻¹)	k_b (M ⁻¹ s ⁻¹)	f_b^c	[Am] _T range (M)	No. of runs
9.80 ± 0.40	- 8.52 ± 3.1 ^d 0	(1.94 ± 0.05) ^b 1.75 ± 0.1 ^e	0.20	0.02 – 0.10	8
10.15 ± 0.05	- 8.67 ± 1.2 0	(2.45 ± 0.02) 2.26 ± 0.1	0.30	0.02 – 0.10	8
10.35 ± 0.05	- 19.9 ± 4.0 0	(3.53 ± 0.08) 3.06 ± 0.2	0.40	0.02 – 0.08	7
10.56 ± 0.05	- 19.3 ± 6.0 0	(4.36 ± 0.13) 3.85 ± 0.19	0.50	0.02 – 0.07	10

^a [26₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^b Calculated from Eq. (3-15)

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

^e Calculated from Eq. (3-15) with $k_o = 0$

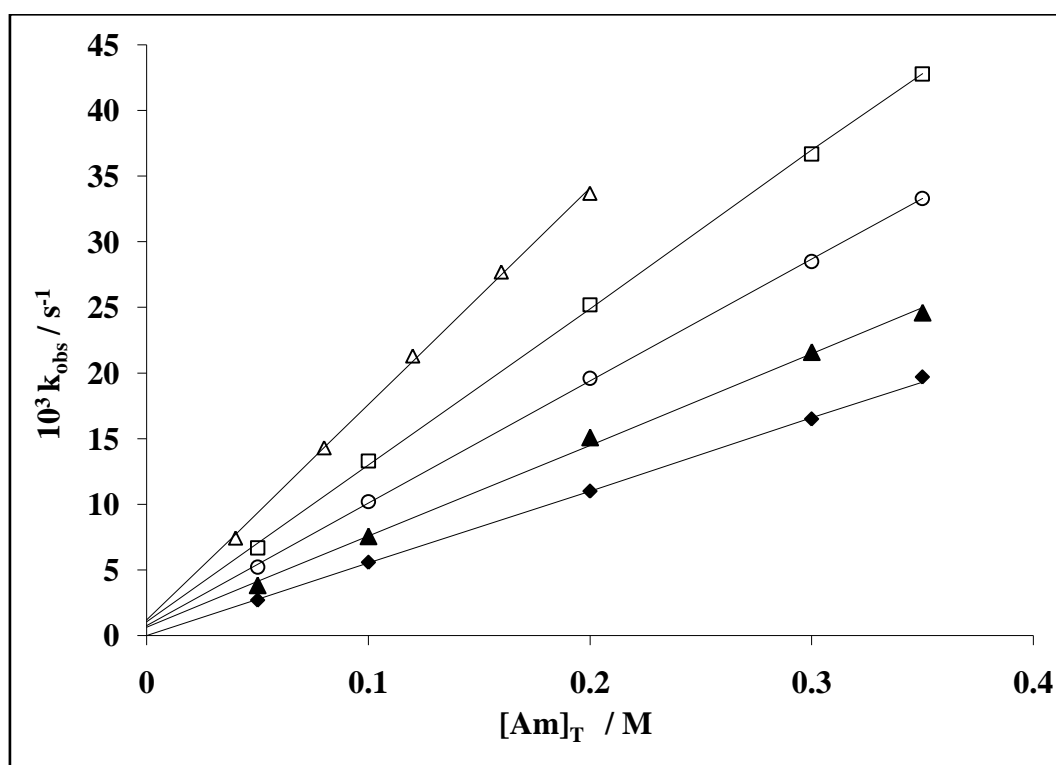


Figure 4-3: Plots of pseudo-first order rate constant k_{obs} versus [Am]_T at different pH for aminolysis of **26** with [Am]_T = [43]_T, $\mu = 0.4$ M at pH 8.28 (■), 8.51 (▲), 8.72 (○), 8.91 (□) and 9.31 (Δ) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-2: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **43** Buffer at Different pH, $\mu = 0.4$ M.^a

pH ^b	$10^4 k_o$ ^b (s ⁻¹)	$10^3 k_b$ ^c (M ⁻¹ s ⁻¹)	f_b ^c	[Am] _T range (M)	No. of runs
8.28 ± 0.07	- 1.10 ± 1.6 ^d 0	(56.0 ± 0.7) ^e 55.2 ± 0.9 ^e	0.25	0.05 – 0.35	5
8.51 ± 0.06	6.44 ± 3.8	69.5 ± 1.7	0.30	0.05 – 0.35	5
8.72 ± 0.06	7.67 ± 2.0	93.0 ± 0.9	0.40	0.05 – 0.35	5
8.91 ± 0.03	10.6 ± 3.0	119.3 ± 1.3	0.50	0.05 – 0.35	5
9.31 ± 0.01	12.0 ± 4.0	164.4 ± 3.1	0.70	0.04 – 0.20	5

^a [26₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^b Calculated from Eq. (3-15)

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

^e Calculated from Eq. (3-15) where $k_o = 0$

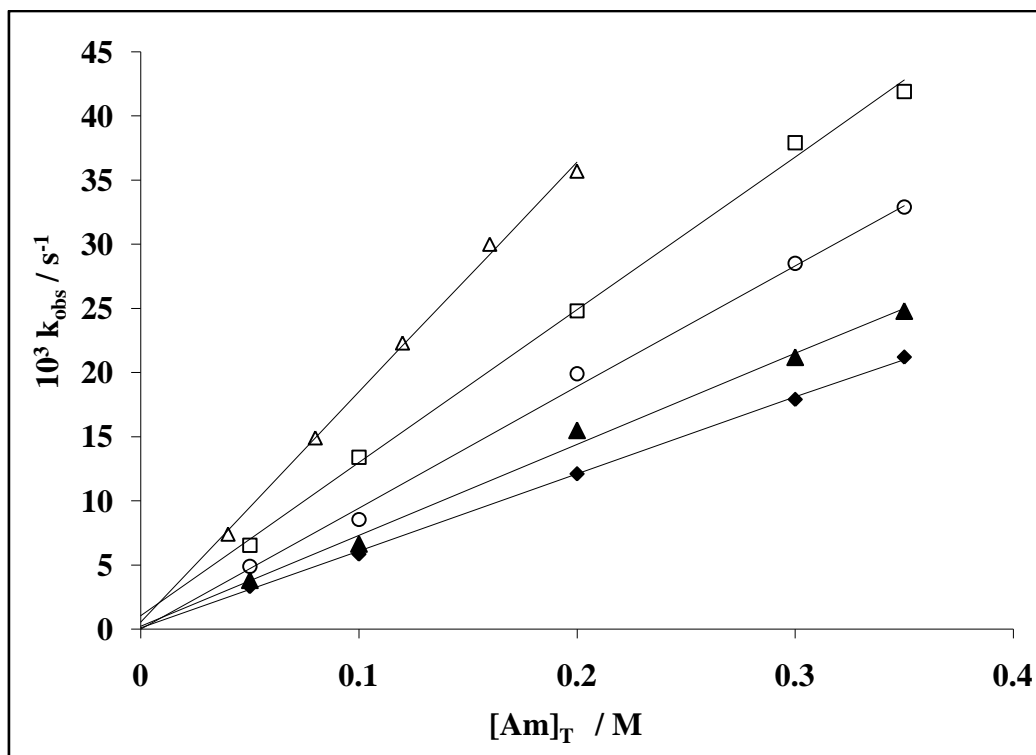


Figure 4-4: Plots of pseudo-first order rate constant k_{obs} versus $[Am]_T$ at different pH for aminolysis of **26** with $[Am]_T = [43]_T$, $\mu = 0.3$ M at pH 8.37 (■), 8.46 (▲), 8.65 (○), 8.86 (□) and 9.25 (Δ) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-3: Values of Kinetic Parameters k_0 and k_b for Aminolysis of **26** in the Presence of **43** Buffer at Different pH, $\mu = 0.3$ M.^a

pH ^b	$10^4 k_0$ ^b (s ⁻¹)	$10^3 k_b$ (M ⁻¹ s ⁻¹)	f_b ^c	[Am] _T range (M)	No. of runs
8.37 ± 0.07	1.02 ± 2.1 ^d	59.8 ± 0.9	0.25	0.05 – 0.35	5
8.46 ± 0.07	2.22 ± 7.0	70.8 ± 3.0	0.30	0.05 – 0.35	5
8.65 ± 0.06	-1.30 ± 7.1 0	(95.4 ± 3.1) ^b 94.3 ± 5.4 ^e	0.40	0.05 – 0.35	5
8.86 ± 0.05	10.4 ± 0.8	119.3 ± 3.5	0.50	0.05 – 0.35	5
9.25 ± 0.01	5.42 ± 6.8	179.3 ± 5.1	0.70	0.04 – 0.20	5

^a [**26**]₀ = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**]₀ = concentration of **26** at t = 0

^b Calculated from Eq. (3-15)

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

^e Calculated from Eq. (3-15) where $k_0 = 0$

The calculated values of k_b at different pH (Tables 4-1 to 4-3) reveal that

$$\text{rate} = k_0 + k_n [\text{Am}] + k_{\text{OH}^-} [\text{Am}][\text{OH}^-] \quad (4-1)$$

$$\begin{aligned} \text{rate} &= k_0 + k_n f_b [\text{Am}]_T + k_{\text{OH}^-} f_b [\text{OH}^-] [\text{Am}]_T \\ &= k_0 + (k_n f_b + k_{\text{OH}^-} f_b [\text{OH}^-]) [\text{Am}]_T \end{aligned} \quad (4-2)$$

Eq. (4-2) comparable with Eq. (3-15) with $k_0 = 0$ and

$$k_b = (k_n + k_{\text{OH}^-} [\text{OH}^-]) f_b \quad (4-3)$$

$$k_b = A1 f_b \quad (4-4)$$

$$A1 = k_n + k_{\text{OH}^-} [\text{OH}^-] \quad (4-5)$$

where $f_b = [\text{Am}]/[\text{Am}]_T$, k_n = second – order rate constant of the cleavage of **26** by nucleophile, k_{OH^-} = third – order rate constant for specific base-catalyzed aminolysis of **26** and $[\text{OH}^-]$ = concentration of hydroxide ion. The values of $[\text{OH}^-]$ were obtained by a

graphical approach described as follows. The pH values of freshly prepared samples containing known concentration of NaOH at desired constant ionic strength at 50 % v/v CH₃CN in mixed aqueous solvent were measured by a digital pH meter at 30°C. These pH versus [NaOH] data and 0.3 or 0.4 M ionic strength are shown graphically in Figs. 4-5 and 4-6, respectively. These observed data at 0.3 or 0.4 M ionic strength were found (by a curve fitting logarithmic trendline drawn using Microsoft Office Excel Program) to fit to respective empirical equations 4-6 and 4-7. The values of pH at different [NaOH]_T/M are shown in Table (A-12) in Appendix. The values of [OH⁻] at different desired pH were calculated from Eqs. 4-6 and 4-7.

$$\text{pH} = 2.062 \ln[\text{NaOH}] + 27.40 \quad (4-6)$$

$$\text{pH} = 2.044 \ln[\text{NaOH}] + 27.18 \quad (4-7)$$

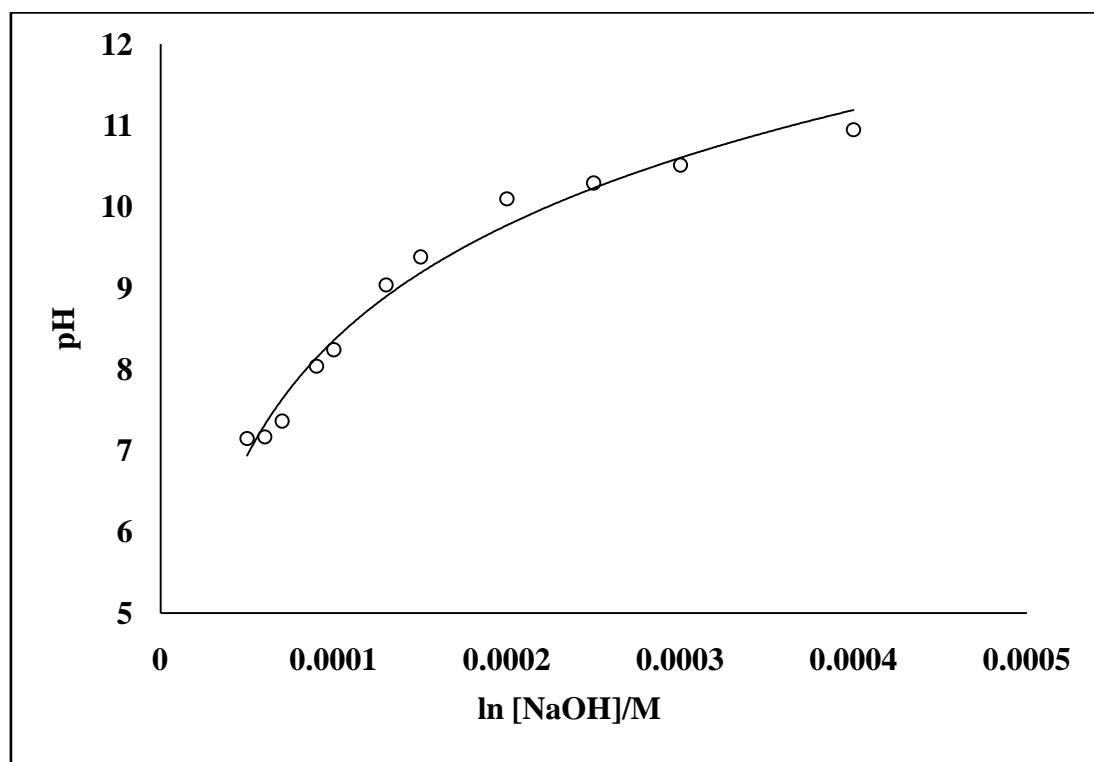


Figure 4-5: Plot of pH versus $\ln [\text{NaOH}]$ for determination of $[\text{OH}^-]$ at 50 % CH₃CN : 50 % H₂O v/v, $\mu = 0.3$ M and $T = 30^\circ$ C. The solid line is drawn using empirical Eq. (4-6).

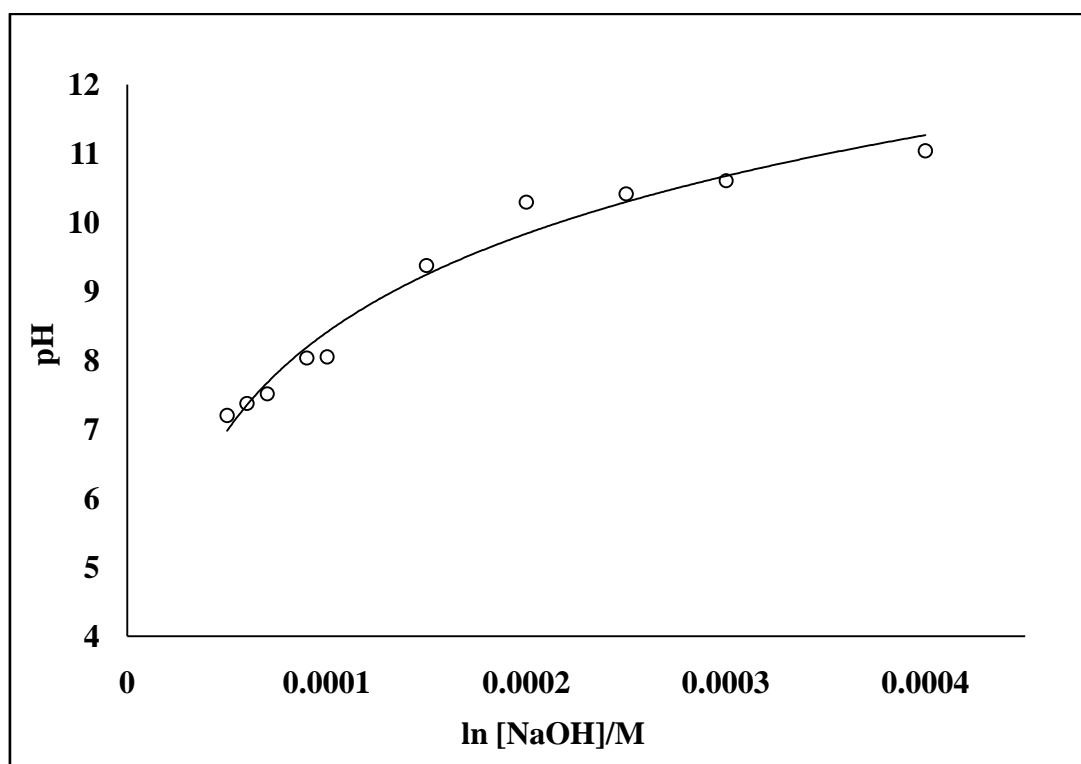


Figure 4-6: Plot of pH versus $\ln [\text{NaOH}]$ for determination of $[\text{OH}^-]$ at 50 % CH_3CN : 50 % H_2O v/v, $\mu = 0.4 \text{ M}$ and $T = 30^\circ \text{ C}$. The solid line is drawn using empirical Eq. (4-7).

The values of k_n and k_{OH^-} , were obtained from the plots of k_b/f_b (i.e. A_1) versus $[\text{OH}^-]$. Such plots for **49** and **43** are shown in Fig. 4-7, where $[\text{OH}^-]$ was calculated using Eqs. (4-6) and (4-7). The values of A_1 and $A_{1\text{cald}}$ are summarized in Table 4-4. Such plots are linear with slope = k_{OH^-} and intercept = k_n for **49** and **43** respectively. The values of k_n and k_{OH^-} for different primary amines together with pK_a values are listed in Table 4-5.

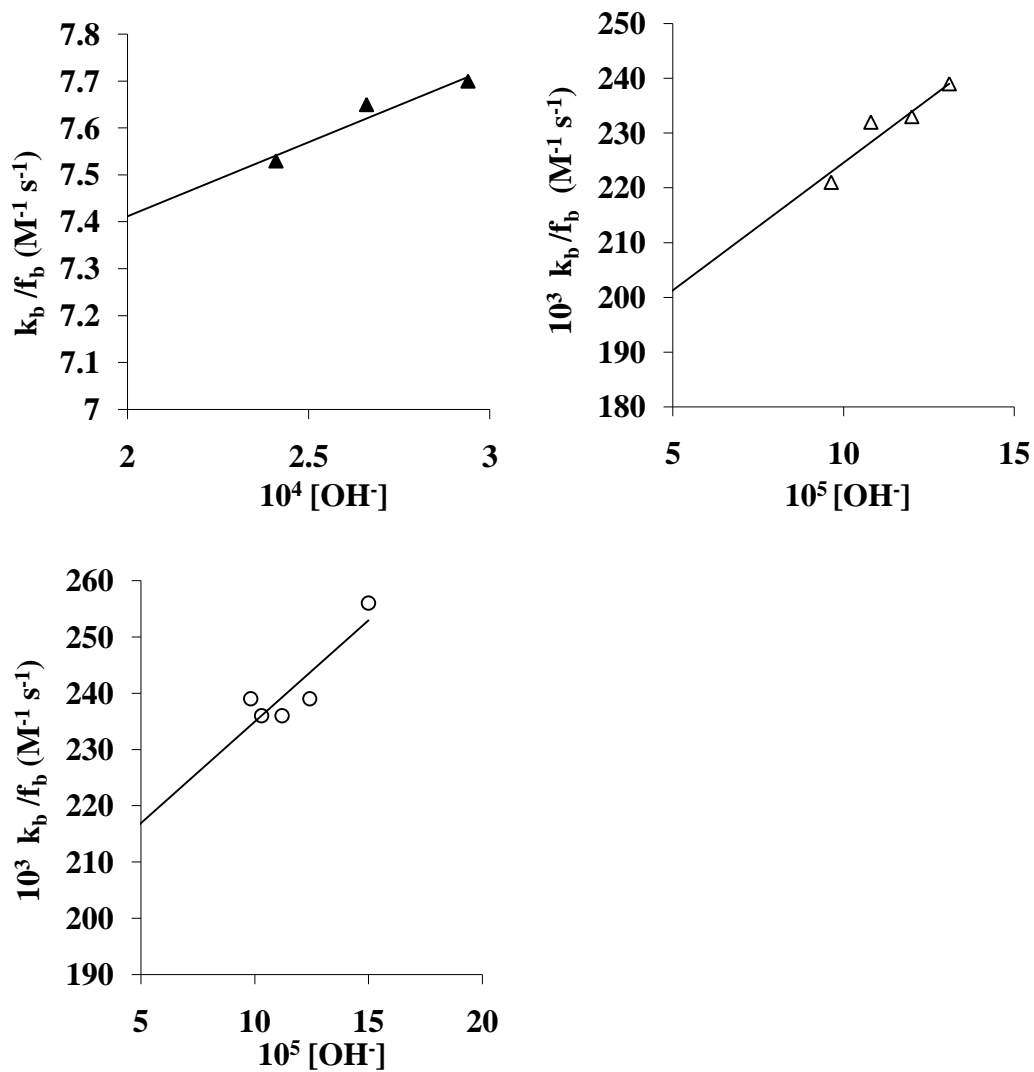


Figure 4-7: Plots of k_b/f_b (A1) versus $[OH^-]$ for aminolysis of **26** in the presence of primary amines: **49** (\blacktriangle)^a, **43** (Δ)^a and **43** (\circ)^b respectively. The solid line are drawn through the calculated data points using Eq. (4-5) as described in text. ^a $\mu = 0.4$ M, ^b $\mu = 0.3$ M

Table 4-4: Values of Kinetic Parameters A1, A1_{calcd} and [OH⁻] for Aminolysis of **26** in the Presence of **49** and **43** Buffers at Different pH.^a

Amines	μ (M)	A1 (M ⁻¹ s ⁻¹) ^b	A1 _{calcd} (M ⁻¹ s ⁻¹) ^b	10 ⁵ [OH ⁻]
49	0.4	8.75 ^c	-	-
		7.53	7.54	24.1 ^d
		7.65	7.62	26.6
		7.70	7.71	29.4
43	0.4	0.221	0.223	9.64
		0.232	0.228	10.8
		0.233	0.234	12.0
		0.239	0.239	13.1
		0.235 ^c	-	-
43	0.3	0.239	0.234	9.82 ^e
		0.236	0.236	10.3
		0.236	0.239	11.2
		0.239	0.244	12.4
		0.256	0.253	15.0

^a [26₀] = 6 x 10⁻⁵ M, T = 30°C, λ = 400 nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^c Value was not included in plot A1 versus [OH⁻]

^d Calculated from Eq. (4-6)

^e Calculated from Eq. (4-7)

Table 4-5: Values of Rate Constant k_n and k_{OH⁻} for Aminolysis of **26** in the Presence of Primary Amines.^a

Primary Amines	pK _a	pK _a ^b	k _n (M ⁻¹ s ⁻¹) ^c	k _{OH⁻} (M ⁻¹ s ⁻¹) ^c
Methylamine ^d	10.85 ^e (10.64) ^{f,g}	10.56	6.78 ± 0.2	3179 ± 866
Benzylamine ^d	9.49 ^h (9.30) ^{f,g}	8.91	(17.9 ± 1.4) x 10 ⁻²	465 ± 125
Benzylamine ⁱ	9.49 ^h	8.86	(19.9 ± 1.9) x 10 ⁻²	358 ± 111

^a [26₀] = 6 x 10⁻⁵ M, T = 30°C, λ = 400 nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^b pK_a = pH at 50 % free base in this study

^c Calculated from Eq. (4-5)

^d μ = 0.4 M

^e Khan M. N., *J. Org. Chem.*, **1983**, *48*, 2046-2052.

^f pK_a protonated amine in water.

^g Bos M., and van der Linden W. E., *Anal. Chim. Acta.*, **1995**, 316(3), 327-62.

^h Frenna F., and Vivono N., *J. Chem. Soc. Perkin Trans. II*, **1985**, 1865-1868. pK_a value in water at 25°C.

ⁱ $\mu = 0.3 \text{ M}$

4.3.2 Effect of Secondary Amines on the Cleavage of **26**

The organic-aqueous cleavage of **26** was studied in buffer solutions of *N,N*-dimethylamine (**50**) within pH range $10.05 \pm 0.10 - 10.66 \pm 0.08$, *N,N*-diethylamine (**37**) within pH range $10.34 \pm 0.05 - 11.10 \pm 0.04$, *N,N*-methylbenzylamine (**51**) within pH range $8.64 \pm 0.07 - 9.63 \pm 0.01$ and *N,N*-ethylbenzylamine (**52**) within pH range $8.81 \pm 0.06 - 9.70 \pm 0.02$. The same kinetic studies were carried out at ionic strength = 0.3 M for buffer solution of *N,N*-methylbenzylamine (**51**) within pH range $8.60 \pm 0.10 - 9.60 \pm 0.06$ and *N,N*-ethylbenzylamine (**52**) within pH range $8.77 \pm 0.08 - 9.61 \pm 0.02$.

The values of pseudo-first-order rate constant, k_{obs} , obtained using nonlinear least-squares technique from Eq. (3-13) for every kinetic run of the reaction between **26** and these amines are shown in Tables (A-4 to A-9) in Appendix. The plots of k_{obs} versus total amine buffer concentration ($[\text{Am}]_{\text{T}}$) at different pH are shown in Figs. 4-6 to 4-11. The values of k_{obs} at different $[\text{Am}]_{\text{T}}$ and a constant pH were treated with Eq. (3-15). The plots with all buffers reveal a linear increase with the increase in total buffer concentration as shown in Figs. 4-6 to 4-11 respectively. The fitting of the observed data to Eq. (3-15) is evident from plots of Figs. 4-8 to 4-13. The values of k_{o} , k_{b} and $[\text{Am}]_{\text{T}}$ are summarized in Tables 4-6 to 4-11.

The values of rate constant, k_{obs} , for aminolysis of **26** at $\mu = 0.4 \text{ M}$ or 0.3 M are almost same. Hence, the reaction of aminolysis of **26** by secondary amines is not affected by ionic strength.

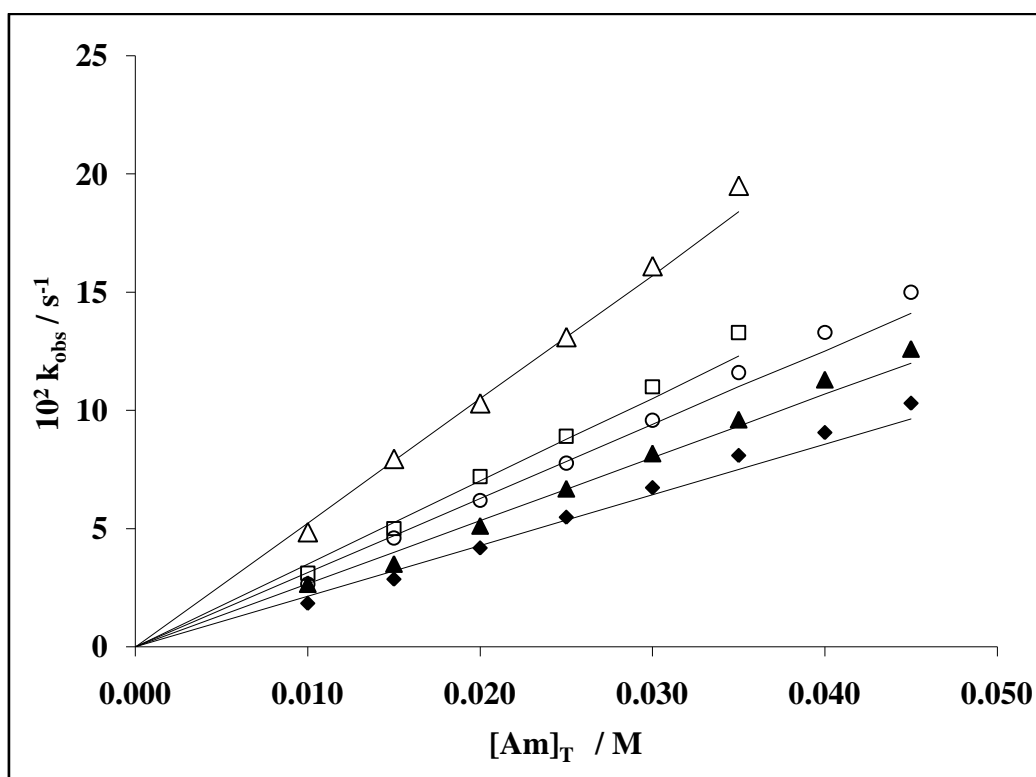


Figure 4-8: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{50}]_{\text{T}}$, $\mu = 0.4$ M at pH 10.05 (\blacksquare), 10.20 (\blacktriangle), 10.29 (\circ), 10.32 (\square) and 10.66 (\triangle) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-6: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **50** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^3 k_o^b$ (s^{-1})	k_b ($\text{M}^{-1}\text{s}^{-1}$)	f_b^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
10.05 \pm 0.10	-6.90 ± 1.0^d 0	2.46 ± 0.03^b 2.14 ± 0.18^e	0.25	0.010 – 0.045	8
10.20 \pm 0.08	-6.27 ± 1.9 0	2.94 ± 0.06 2.67 ± 0.16	0.30	0.010 – 0.045	8
10.29 \pm 0.09	-8.54 ± 1.2 0	3.52 ± 0.04 3.14 ± 0.22	0.35	0.010 – 0.045	8
10.32 \pm 0.10	-9.98 ± 1.8 0	4.04 ± 0.08 3.51 ± 0.20	0.40	0.010 – 0.035	6
10.66 \pm 0.08	-9.55 ± 3.6 0	5.74 ± 0.15 5.25 ± 0.25	0.50	0.010 – 0.035	6

^a $[\text{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\text{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15)

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

^e Calculated from Eq. (3-15) with $k_o = 0$

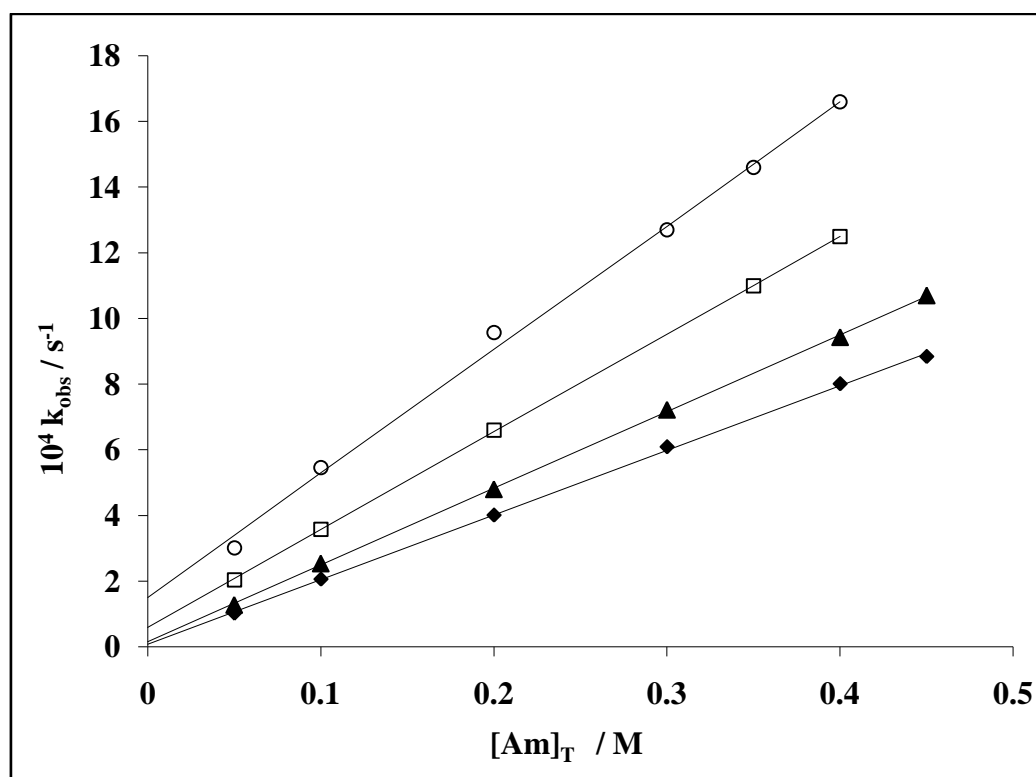


Figure 4-9: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{37}]_{\text{T}}$, $\mu = 0.4$ M at pH 10.34 (\blacksquare), 10.44 (\blacktriangle), 10.77 (\square) and 11.10 (\circ) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-7: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **37** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^4 k_o$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
10.34 ± 0.05	0.81 ± 0.7 ^d	19.7 ± 0.20 ^b	0.30	0.05 – 0.45	8
10.44 ± 0.04	1.52 ± 0.5	23.4 ± 0.20	0.40	0.05 – 0.45	6
10.77 ± 0.04	5.88 ± 0.3	29.8 ± 0.10	0.50	0.05 – 0.40	5
11.10 ± 0.04	15.0 ± 3.0	37.8 ± 1.10	0.70	0.05 – 0.40	6

^a $[\text{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\text{26}_0]$ = concentration of **26** at $t = 0$.

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

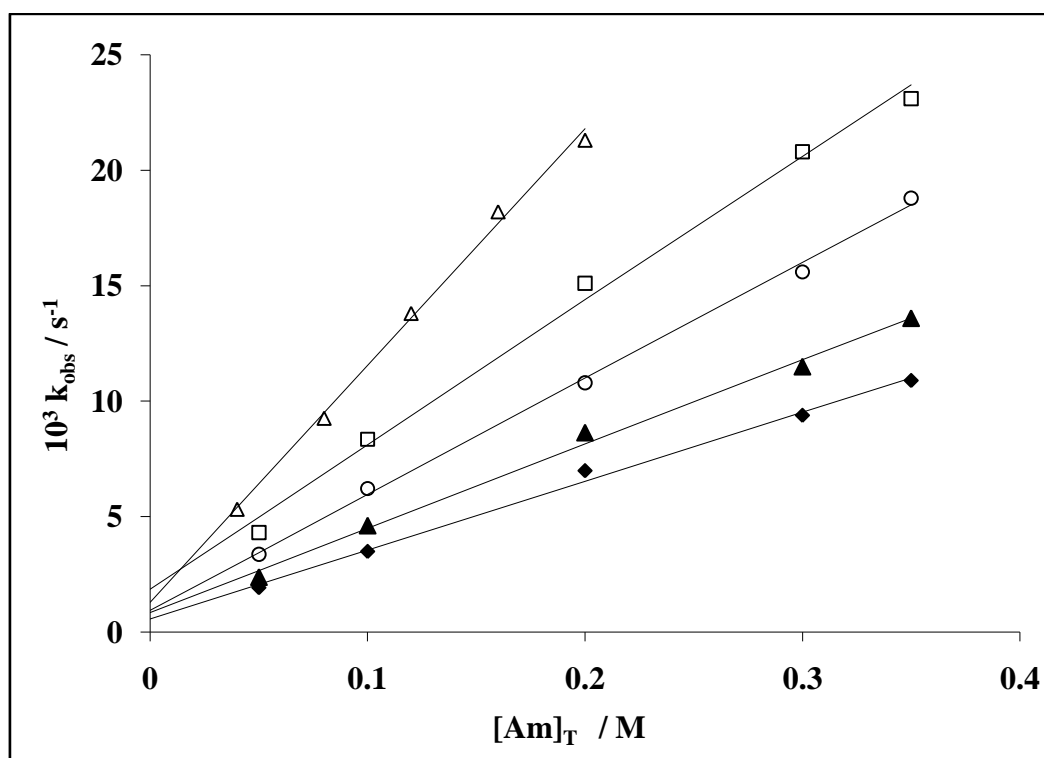


Figure 4-10: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\mathbf{51}]_{\text{T}}$, $\mu = 0.4$ M at pH 8.64 (\blacksquare), 8.79 (\blacktriangle), 9.00 (\circ), 9.22 (\square) and 9.63 (\triangle) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-8: Values of Kinetic Parameters k_0 and k_b for Aminolysis of **26** in the Presence of **51** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^4 k_0$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
8.64 ± 0.07	5.68 ± 1.0 ^d	29.8 ± 1.2 ^b	0.25	0.05 – 0.035	5
8.79 ± 0.07	8.48 ± 3.4	36.5 ± 1.5	0.30	0.05 – 0.35	5
9.00 ± 0.06	9.39 ± 3.1	50.1 ± 1.3	0.40	0.05 – 0.35	5
9.22 ± 0.05	18.5 ± 6.7	62.5 ± 2.9	0.50	0.05 – 0.35	5
9.63 ± 0.01	12.9 ± 5.6	102.7 ± 4.2	0.70	0.04 – 0.20	5

^a $[\mathbf{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\mathbf{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15)

^c f_b = fraction of free amine base

^d Error limits are standard deviations

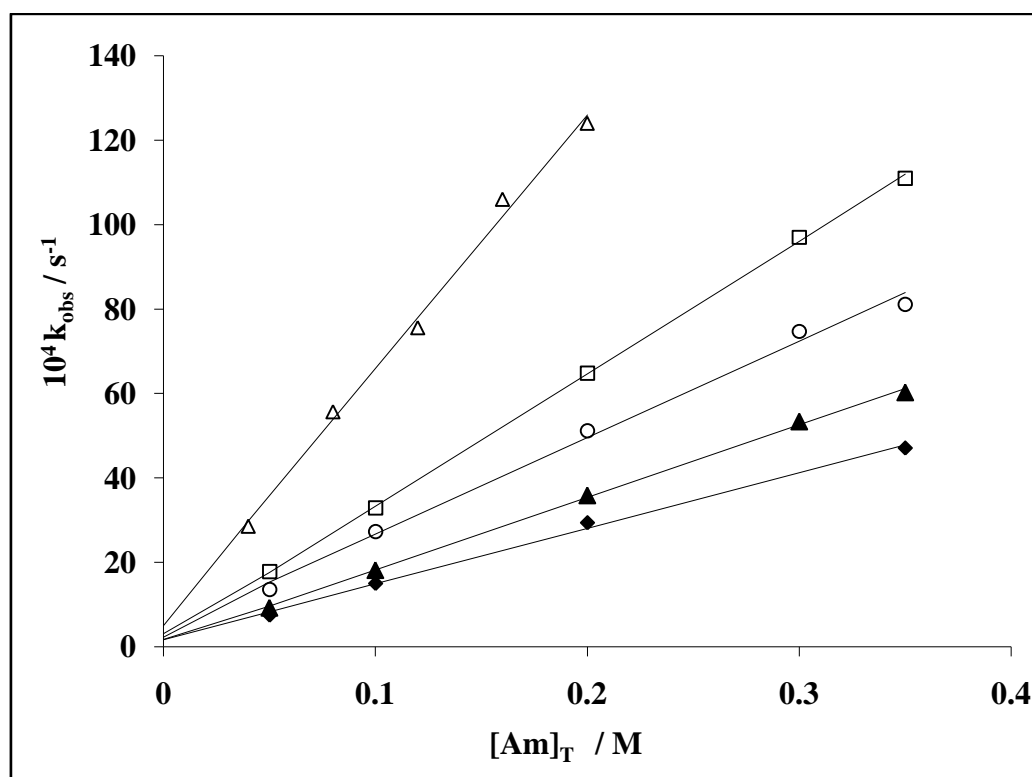


Figure 4-11: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{52}]_{\text{T}}$, $\mu = 0.4$ M at pH 8.72 (\blacksquare), 8.81 (\blacktriangle), 9.11 (\circ), 9.31 (\square) and 9.71 (\triangle) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-9: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **52** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^5 k_o$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
8.72 ± 0.07	1.68 ± 1.1 ^d	1.32 ± 0.05 ^b	0.25	0.05 – 0.035	5
8.81 ± 0.06	1.04 ± 0.7	1.72 ± 0.03	0.30	0.05 – 0.35	5
9.11 ± 0.07	3.84 ± 2.2	2.29 ± 0.10	0.40	0.05 – 0.35	5
9.31 ± 0.06	1.96 ± 0.7	3.14 ± 0.03	0.50	0.05 – 0.35	5
9.71 ± 0.03	2.99 ± 7.8	5.51 ± 0.60	0.70	0.04 – 0.20	5

^a $[\mathbf{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\mathbf{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

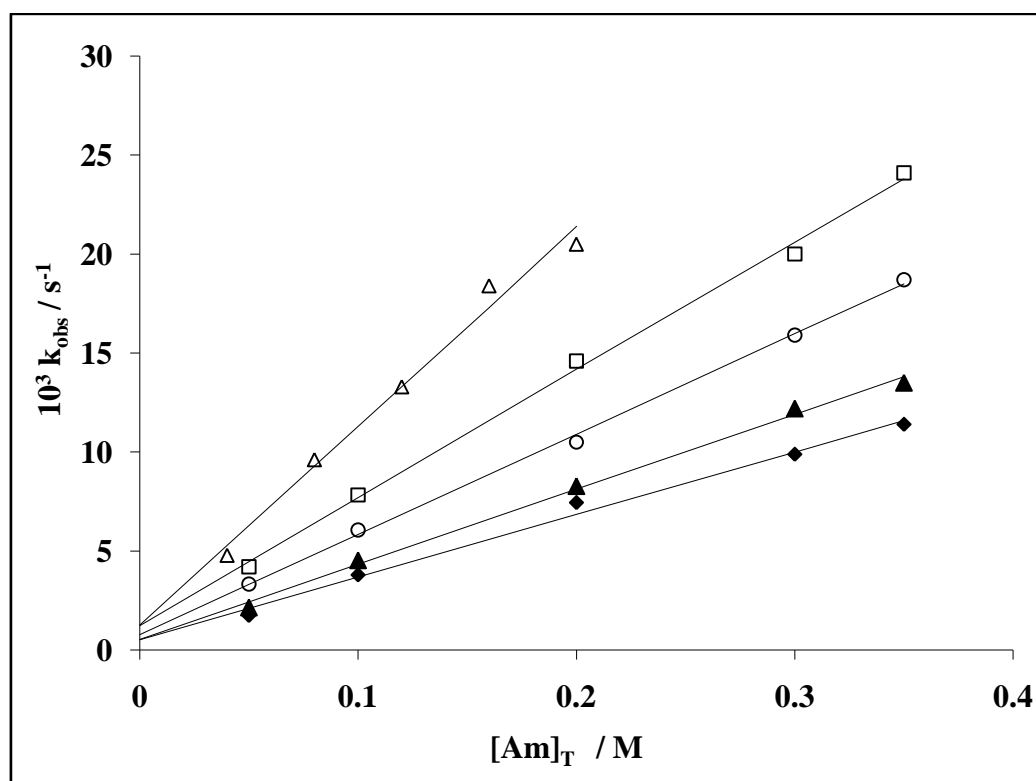


Figure 4-12: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{51}]_{\text{T}}$, $\mu = 0.3$ M at pH 8.60 (\blacksquare), 8.71 (\blacktriangle), 8.97 (\circ), 9.16 (\square) and 9.60 (\triangle) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-10: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **51** Buffer at Different pH, $\mu = 0.3$ M.^a

pH	$10^4 k_o$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
8.60 ± 0.10	5.30 ± 3.9 ^d	31.6 ± 0.1 ^b	0.25	0.05 – 0.035	5
8.71 ± 0.09	5.34 ± 3.0	38.0 ± 1.3	0.30	0.05 – 0.35	5
8.97 ± 0.07	7.76 ± 2.6	50.6 ± 1.1	0.40	0.05 – 0.35	5
9.16 ± 0.06	12.3 ± 4.4	64.6 ± 1.9	0.50	0.05 – 0.35	5
9.60 ± 0.02	12.6 ± 9.06	100.5 ± 6.8	0.70	0.04 – 0.20	5

^a $[\text{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\text{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

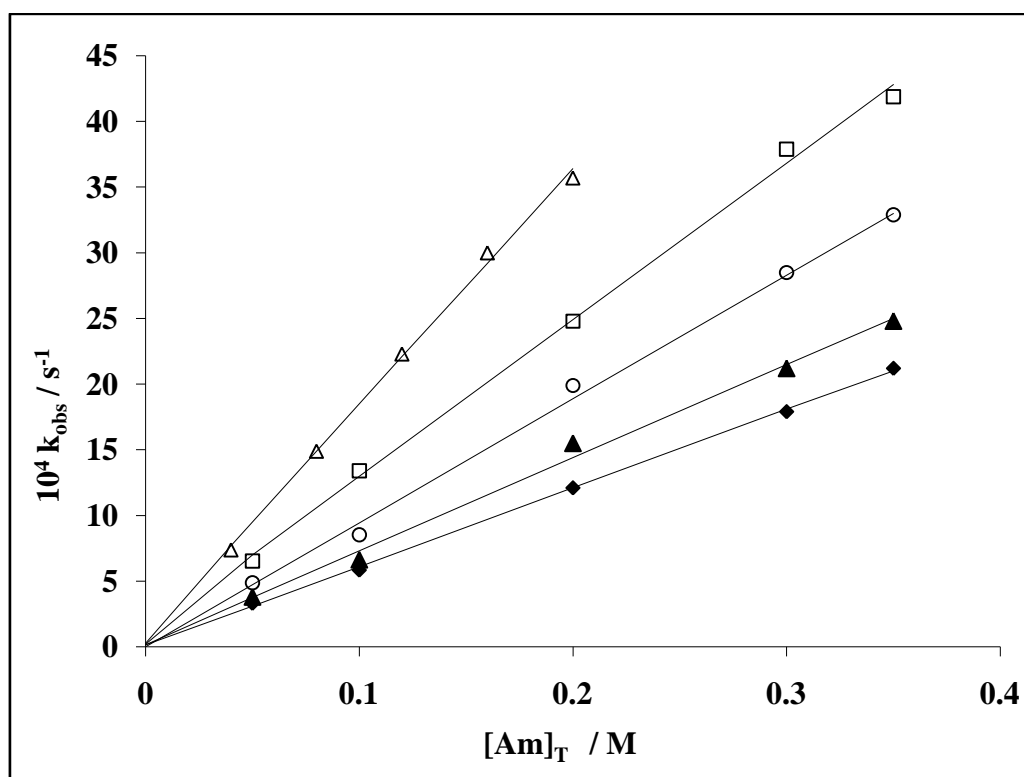


Figure 4-13: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{52}]_{\text{T}}$ $\mu = 0.3$ M at pH 8.65 (\blacksquare), 8.77 (\blacktriangle), 8.97 (\circ), 9.21 (\square) and 9.61 (\triangle) respectively. The solid lines are drawn through the calculated data points using Eq. (3-15) as described in the text.

Table 4-11: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **52** Buffer at Different pH, $\mu = 0.3$ M.^a

pH	$10^6 k_o$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
8.65 ± 0.09	0.07 ± 9.8 ^d	1.47 ± 0.04	0.25	0.05 – 0.35	5
8.77 ± 0.08	14.7 ± 3.4	1.68 ± 0.01	0.30	0.05 – 0.35	5
8.97 ± 0.08	-12.4 ± 28	(2.37 ± 0.10) ^b	0.40	0.05 – 0.35	5
	0	2.31 ± 0.20 ^e			
9.21 ± 0.08	20.6 ± 16.0	3.18 ± 0.07	0.50	0.05 – 0.35	5
9.61 ± 0.02	27.9 ± 7.0	4.46 ± 0.05	0.70	0.04 – 0.20	5

^a $[\text{26}_0] = 6 \times 10^{-5}$ M, $T = 30^\circ\text{C}$, $\lambda = 400$ nm and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\text{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

^e Calculated from Eq. (3-15) where $k_o = 0$

The values of k_n and k_{OH^-} were obtained from the plots of A_1 versus $[OH^-]$. The plots for these amines are shown in Fig. 4-14, where $[OH^-]$ was calculated using Eqs. (4-6) and (4-7). The values of A_1 and $A_{1\text{cald}}$ are summarized in Table 4-12. Such plots are linear with slope = k_{OH^-} and intercept = k_n for the aminolysis of **26** by **50**, **51** and **52** respectively. The calculated values for k_n and k_{OH^-} for different secondary amines together with pK_a values are listed in Table 4-13.

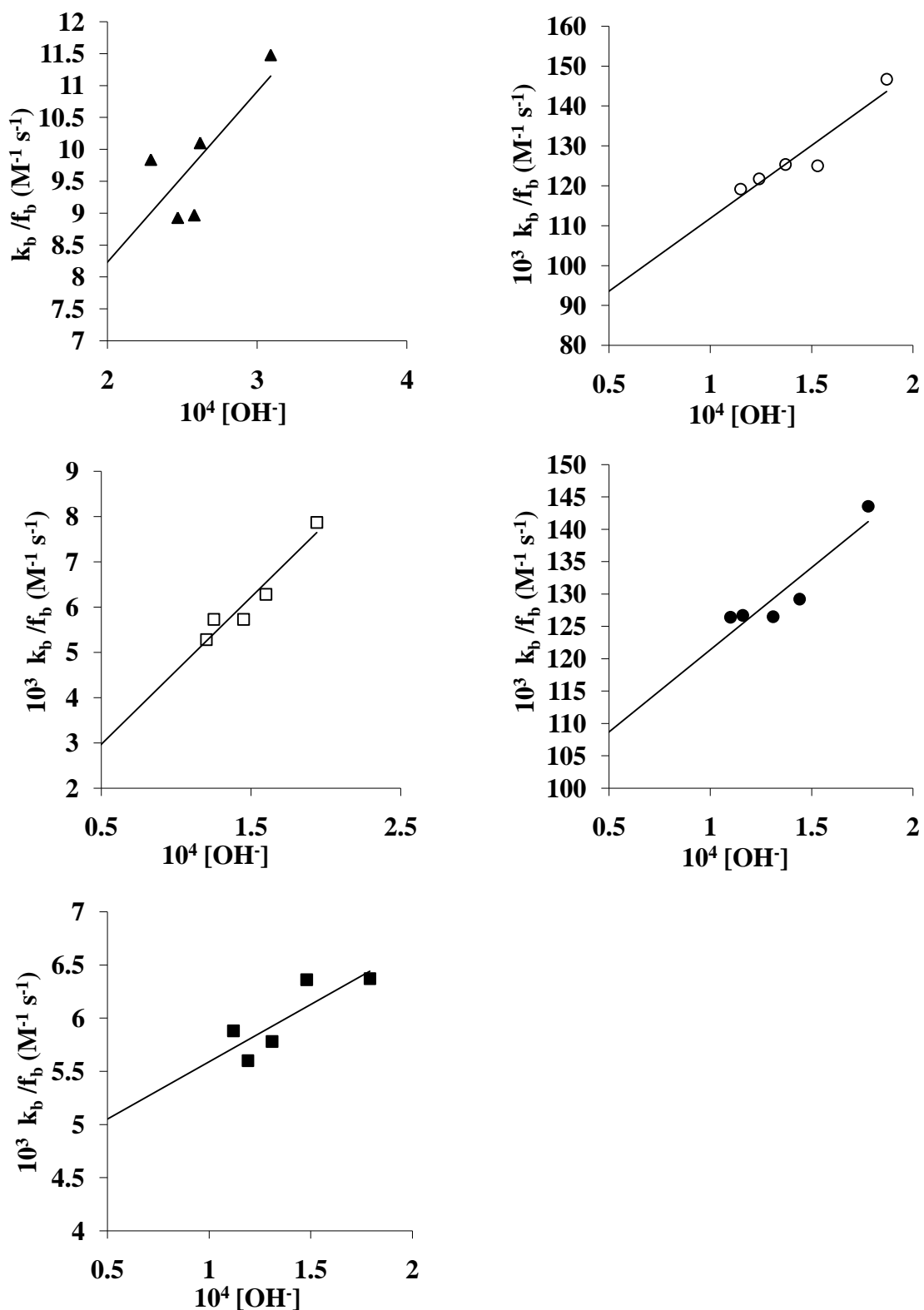


Figure 4-14: Plots of k_b/f_b (A1) versus $[\text{OH}^-]$ for aminolysis of **26** in the presence of secondary amines: **50** (\blacktriangle)^a, **51** (\circ)^a, **52** (\square)^a, **51** (\bullet)^b, and **52** (\blacksquare)^b respectively. The solid lines are drawn through the calculated data points using Eq. (4-5) as described in text. ^a $\mu = 0.4 \text{ M}$, ^b $\mu = 0.3 \text{ M}$

Table 4-12 : Values of Kinetic Parameters A1, A1_{calcd} and [OH⁻] for Aminolysis of **26** in the Presence of **50**, **37**, **51** and **52** Buffers at Different pH.^a

Amines	μ (M)	A1 (M ⁻¹ s ⁻¹) ^b	A1 _{calcd} (M ⁻¹ s ⁻¹) ^b	10 ⁴ [OH ⁻]
50	0.4	9.84	9.01	2.29 ^c
		8.93	9.49	2.47
		8.97	9.78	2.58
		10.10	9.89	2.62
		11.48	11.15	3.09
37	0.4	0.0657 ^d		
		0.0585		
		0.0596		
		0.0540		
51	0.4	0.1192	0.1173	1.15
		0.1217	0.1206	1.24
		0.1253	0.1253	1.37
		0.1250	0.1312	1.53
		0.1467	0.1436	1.87
	0.3	0.1264	0.1239	1.10 ^e
		0.1267	0.1255	1.16
		0.1265	0.1293	1.31
		0.1292	0.1326	1.44
		0.1436	0.1412	1.78
52	0.4	0.00528	0.00525	1.20
		0.00573	0.00541	1.25
		0.00573	0.00605	1.45
		0.00628	0.00654	1.60
		0.00787	0.00765	1.94
	0.3	0.00588	0.00572	1.12
		0.00560	0.00579	1.19
		0.00578	0.00593	1.31
		0.00636	0.00611	1.48
		0.00637	0.00644	1.79

^a [26₀] = 6 x 10⁻⁵ M, T = 30°C, λ = 400 nm, 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^b Calculated from Eq. (4-5)

^c Calculated from Eq. (4-7)

^d Data was not included in plot of A1 versus [OH⁻].

^e Calculated from Eq. (4-6)

Table 4-13: Values of Rate Constant k_n and k_{OH^+} for Aminolysis of **26** in the Presence of Secondary Amines.^a

Secondary Amines	pK _a	pK _a ^b	k_n (M ⁻¹ s ⁻¹) ^c	k_{OH^+} (M ⁻¹ s ⁻¹) ^c
<i>N,N</i> -Dimethylamine ^d	11.05 ^e (10.72) ^{f, g}	10.66	2.90 ± 3.4	26693 ± 13107
<i>N,N</i> -Diethylamine ^d	11.07 ^h (11.00) ^g	10.77	(59.5 ± 4.8) × 10 ⁻³ ⁱ	-
<i>N,N</i> -Methylbenzylamine ^d	9.63 ^h	9.22	(7.53 ± 1.1) × 10 ⁻²	365 ± 74
<i>N,N</i> -Methylbenzylamine ^j	9.63 ^h	9.16	(9.61 ± 0.8) × 10 ⁻²	253 ± 61
<i>N,N</i> -Ethylbenzylamine ^d	9.83 ^h	9.31	(1.36 ± 0.8) × 10 ⁻³	32 ± 6
<i>N,N</i> -Ethylbenzylamine ^j	9.83 ^h	9.61	(4.48 ± 0.6) × 10 ⁻³	11 ± 4

^a [**26**₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm, 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**₀] = concentration of **26** at t = 0

^b pK_a = pH at 50% free base in this study.

^c Calculated from Eq. (4-5)

^d μ = 0.4 M

^e Khan M.N., *J. Chem. Soc. Perkin Trans. II*, **1989**, 199-208.

^f pK_a of protonated amine in water.

^g Bos M and van der Linden W. E., *Anal. Chim. Acta.*, **1995**, 316(3), 327-62.

^h Frenna F., and Vivono N., *J. Chem. Soc. Perkin Trans. II*, **1985**, 1865-1868. pK_a value in water at 25°C.

ⁱ k_n = Average values of A1.

^j μ = 0.3 M

4.3.3 Effect of Tertiary Amine on the Cleavage of **26**

The organic-aqueous cleavage of **26** was studied in buffer solutions of *N,N*-dimethylbenzylamine (**53**) within pH range 8.07 ± 0.07 - 8.65 ± 0.06. The values of pseudo-first-order rate constant, k_{obs} , were obtained using nonlinear least-squares technique from Eq (2-13). The observed data for each kinetic run of reaction between **26** with **53** are summarized in Tables (A-10) in Appendix.

The plot of k_{obs} versus total amine buffer concentrations ([Am]_T) at different pH are shown in Fig. 4-15. The values of k_{obs} at different [Am]_T and a constant pH were treated with Eq. (3-15) (Fig. 4-15). The values of k_o , k_b and [Am]_T are

summerized in Table 4-14. The values of A_1 were shown in Table 4-15. The values of k_n for tertiary amine together with pK_a values are listed in Table 4-16.

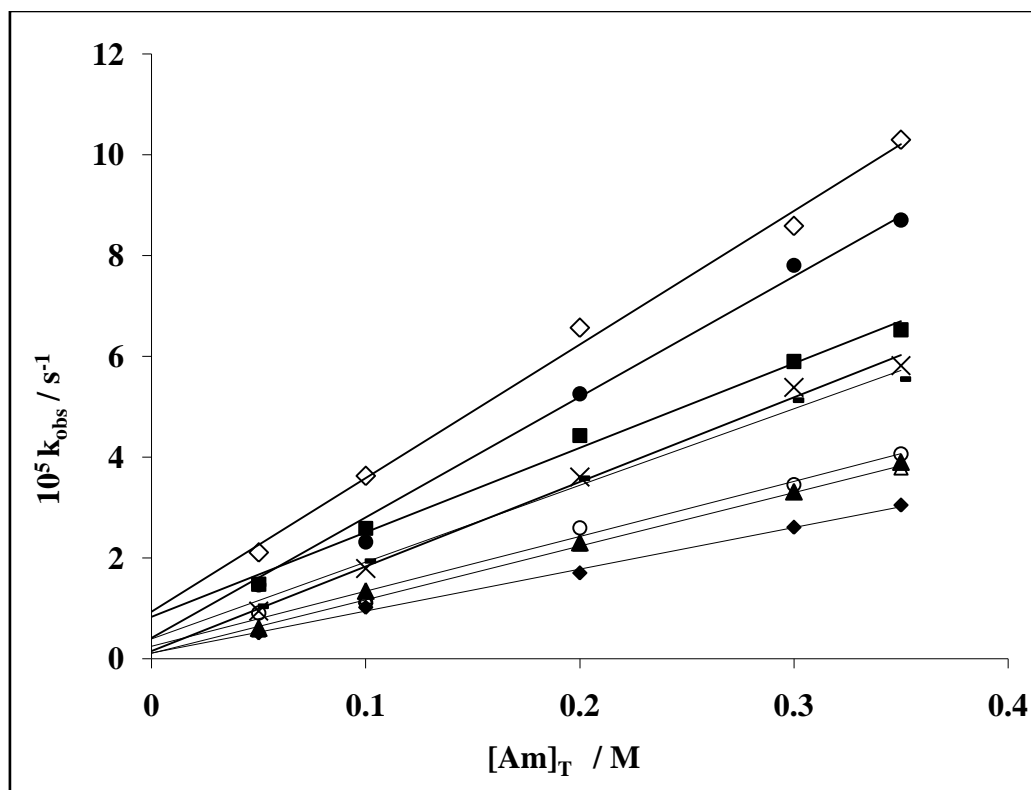


Figure 4-15: Plots of pseudo-first order rate constant k_{obs} versus $[Am]_T$ at different pH for aminolysis of **26** with $[Am]_T = [53]_T$ at pH 8.07 (◆), 8.20 (Δ), 8.16 (○), 8.34 (▲), 8.35 (—), 8.50 (■), 8.45 (×), 8.76 (●) and 8.65 (◇) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4$ M

Table 4-14: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **53** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^6 k_o$ (s ⁻¹) ^b	$10^4 k_b$ (M ⁻¹ s ⁻¹)	f_b ^c	[Am] _T range (M)	No. of runs
8.07 ± 0.07	1.18 ± 0.6 ^d	0.83 ± 0.03 ^b	0.25	0.05 – 0.35	5
8.16 ± 0.07	1.04 ± 0.7	1.09 ± 0.07	0.30	0.05 – 0.35	5
8.20 ± 0.07	1.73 ± 0.8	1.06 ± 0.03	0.30	0.05 – 0.35	5
8.34 ± 0.08	1.12 ± 0.6	1.06 ± 0.02	0.40	0.05 – 0.35	5
8.35 ± 0.08	3.98 ± 1.7	1.52 ± 0.08	0.40	0.04 – 0.20	5
8.45 ± 0.08	1.55 ± 1.6	1.68 ± 0.07	0.50	0.05 – 0.35	5
8.50 ± 0.07	8.37 ± 1.9	1.67 ± 0.08	0.50	0.05 – 0.35	5
8.76 ± 0.02	8.32 ± 2.2	2.52 ± 0.1	0.60	0.05 – 0.35	5
8.65 ± 0.06	9.34 ± 2.5	2.65 ± 0.1	0.60	0.05 – 0.35	5

^a [**26**]₀ = 6 x 10⁻⁵ M, T = 30°C, $\lambda = 400$ nm and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**]₀ = concentration of **26** at t = 0

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

Table 4-15 : Values of Kinetic Parameters A1 for Aminolysis of **26** in the Presence of **53** Buffer at Different pH, $\mu = 0.4$ M.^a

pH	$10^4 A1$ (M ⁻¹ s ⁻¹) ^b
8.07 ± 0.07	3.32
8.16 ± 0.07	3.63
8.20 ± 0.07	3.53
8.34 ± 0.08	2.65
8.35 ± 0.08	3.80
8.45 ± 0.08	3.36
8.50 ± 0.07	3.34
8.76 ± 0.02	4.20 ^c
8.65 ± 0.06	4.42 ^c

^a [**26**]₀ = 6 x 10⁻⁵ M, T = 30°C, $\lambda = 400$ nm, $\mu = 0.4$ M and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**]₀ = concentration of **26** at t = 0

^b A1 = k_b/f_b

^c Value was not included in determine k_n .

Table 4-16: Value of Rate Constant, k_n for Aminolysis of **26** in the Presence of Tertiary Amine ^a

Tertiary Amine	pK _a	pK _a	10 ⁴ k _n (M ⁻¹ s ⁻¹) ^b
<i>N,N</i> -Dimethylbenzylamine	9.03 ^c (8.88) ^{e,f}	8.48 ^d	3.37 ± 0.4

^a [26₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm, μ = 0.4 M, 50 % v/v CH₃CN in mixed aqueous reaction mixture. [26₀] = concentration of **26** at t = 0

^b k_n = Average values of A1.

^c protonated amine in water at 25 °C, μ = 0

^d pK_a = pH_{av} at 50 % free base in this study.

^e Hine J., and Khan M. N., *Indian J. Chem. Sec. B*, **1992**, 427-435.

^f Frenna F., and Vivono N., *J. Chem. Soc. Perkin Trans. II*, **1985**, 1865-1868. pK_a value in water at 25°C.

4.3.4 Effect of Amino Alcohol on the Cleavage of **26**

The organic-aqueous cleavage of **26** was studied in buffer solutions of *N,N*-(diethylaminomethyl)benzyl alcohol (**35**) within the pH range 7.95 ± 0.06 - 8.89 ± 0.06. The values of pseudo-first-order rate constant, k_{obs}, obtained using nonlinear least-squares technique from Eq. (3-13) for every kinetic runs of reaction between **26** with **35** are summerized in Tables (A-11) in Appendix.

The plot of k_{obs}, versus total amine buffer concentrations ([Am]_T) at different pH are shown in Fig. 4-16. The values of k_{obs} at different [Am]_T and a constant pH were treated with Eq. (3-15) (Fig. 4-16). The values of k_o, k_b and [Am]_T are summerized in Table 4-17. The values of A1 were shown in Table 4-18. The values of k_n for tertiary amine together with pK_a values are listed in Table 4-19.

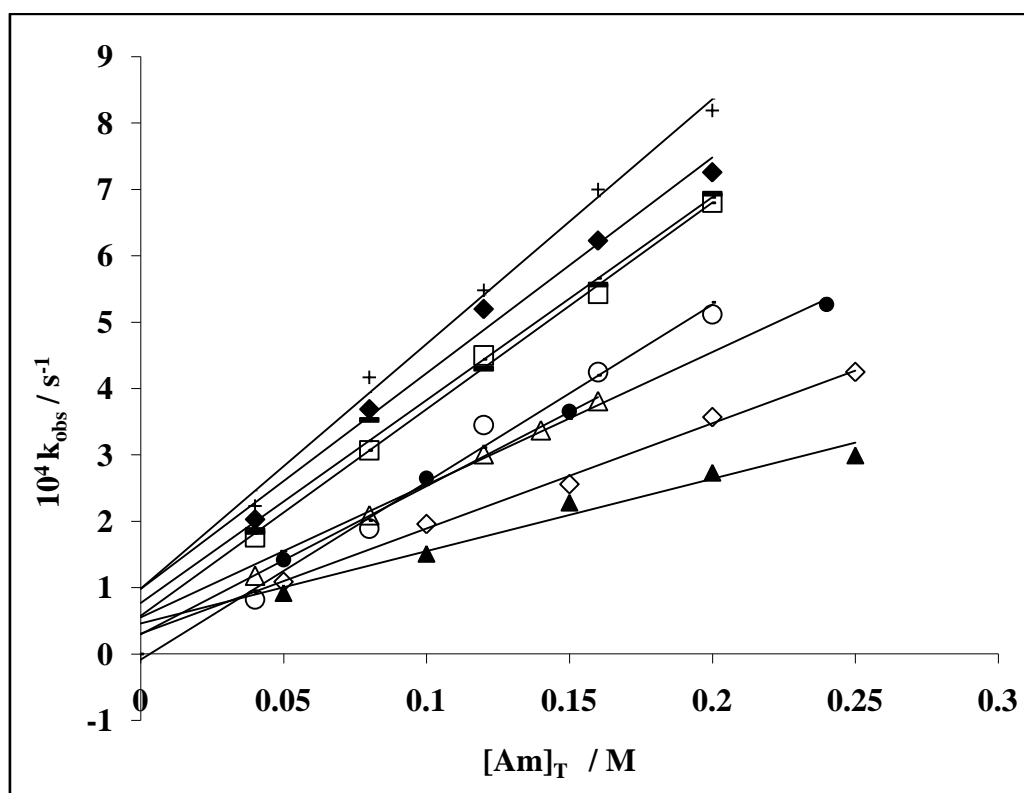


Figure 4-16: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{35}]_{\text{T}}$ at pH 7.91 (\blacktriangle), 7.99 (\diamond), 8.21 (Δ), 8.22 (\bullet), 8.27 (\circ), 8.56 (\square), 8.68 (\blacksquare), 8.93 ($+$), and 8.85 (\blacklozenge) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4 \text{ M}$

Table 4-17: Values of Kinetic Parameters k_o and k_b for Aminolysis of **26** in the Presence of **35** Buffer at Different pH, $\mu = 0.4 \text{ M}$. ^a

pH	$10^5 k_o$ (s^{-1}) ^b	$10^3 k_b$ ($\text{M}^{-1}\text{s}^{-1}$)	f_b ^c	$[\text{Am}]_{\text{T}}$ range (M)	No. of runs
7.99 ± 0.07	3.07 ± 1.0 ^d	1.59 ± 0.06 ^b	0.35	0.05 – 0.25	5
7.91 ± 0.07	4.78 ± 1.8	1.07 ± 0.11	0.35	0.05 – 0.25	5
8.27 ± 0.03	1.80 ± 2.5	2.50 ± 0.30	0.50	0.04 – 0.20	5
8.21 ± 0.05	3.14 ± 0.4	2.21 ± 0.04	0.50	0.04 – 0.16	5
8.22 ± 0.08	5.45 ± 1.6	2.00 ± 0.10	0.50	0.05 – 0.24	4
8.68 ± 0.05	7.64 ± 2.4	3.06 ± 0.20	0.70	0.04 – 0.20	5
8.56 ± 0.05	5.80 ± 1.4	3.11 ± 0.10	0.70	0.04 – 0.20	5
8.85 ± 0.04	9.82 ± 2.9	3.25 ± 0.20	0.80	0.04 – 0.20	5
8.93 ± 0.03	9.89 ± 2.4	3.69 ± 0.20	0.80	0.04 – 0.20	5

^a $[\text{26}_0] = 6 \times 10^{-5} \text{ M}$, $T = 30^\circ\text{C}$, $\lambda = 400 \text{ nm}$ and 50 % v/v CH_3CN in mixed aqueous reaction mixture. $[\text{26}_0]$ = concentration of **26** at $t = 0$

^b Calculated from Eq. (3-15).

^c f_b = fraction of free amine base.

^d Error limits are standard deviations.

Table 4-18 : Values of Kinetic Parameter A1 for Aminolysis of **26** in the Presence of **35** Buffer at Different pH. ^a

pH	$10^3 A1$ ($M^{-1}s^{-1}$) ^b
7.99 ± 0.07	4.54
7.91 ± 0.07	3.06 ^c
8.27 ± 0.03	5.00
8.21 ± 0.05	4.42
8.22 ± 0.08	4.00
8.68 ± 0.05	4.37
8.56 ± 0.05	4.44
8.85 ± 0.04	4.06
8.93 ± 0.03	4.61

^a [**26**₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm, μ = 0.4 M and 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**₀] = concentration of **26** at t = 0

^b A1 = k_b/f_b

^c Value was no include in determine k_n.

Table 4-19: Values of Rate Constant, k_n for Aminolysis of **26** in the Presence of Amino Alcohol. ^a

Amino Alcohol	pK _a ^b	$10^3 k_n$ ($M^{-1}s^{-1}$) ^c
<i>o</i> -HOCH ₂ C ₆ H ₄ CH ₂ N(CH ₂ CH ₃) ₂	8.23	4.40 ± 0.3

^a [**26**₀] = 6 × 10⁻⁵ M, T = 30°C, λ = 400 nm, μ = 0.4 M, 50 % v/v CH₃CN in mixed aqueous reaction mixture. [**26**₀] = concentration of **26** at t = 0

^b pK_a = pH_{av} at 50 % free base in this study.

^c k_n = Average values of A1.

4.4 Discussions

In general, a wide variety of weak bases, like amines and oxygen anions, can catalyze the hydrolysis of carboxylic acid esters. The cleavage of ester involved either general base, general acid (GA-GB) catalysis or nucleophilic catalysis by buffer components.³⁰⁻³⁶ It has also been reported that two mechanisms may occur concurrently.³⁰ As evident from the results, here we can divide our discussions into

three parts 1) primary and secondary amines, 2) tertiary amine, 3) amino alcohol and 4) Bronsted plot.

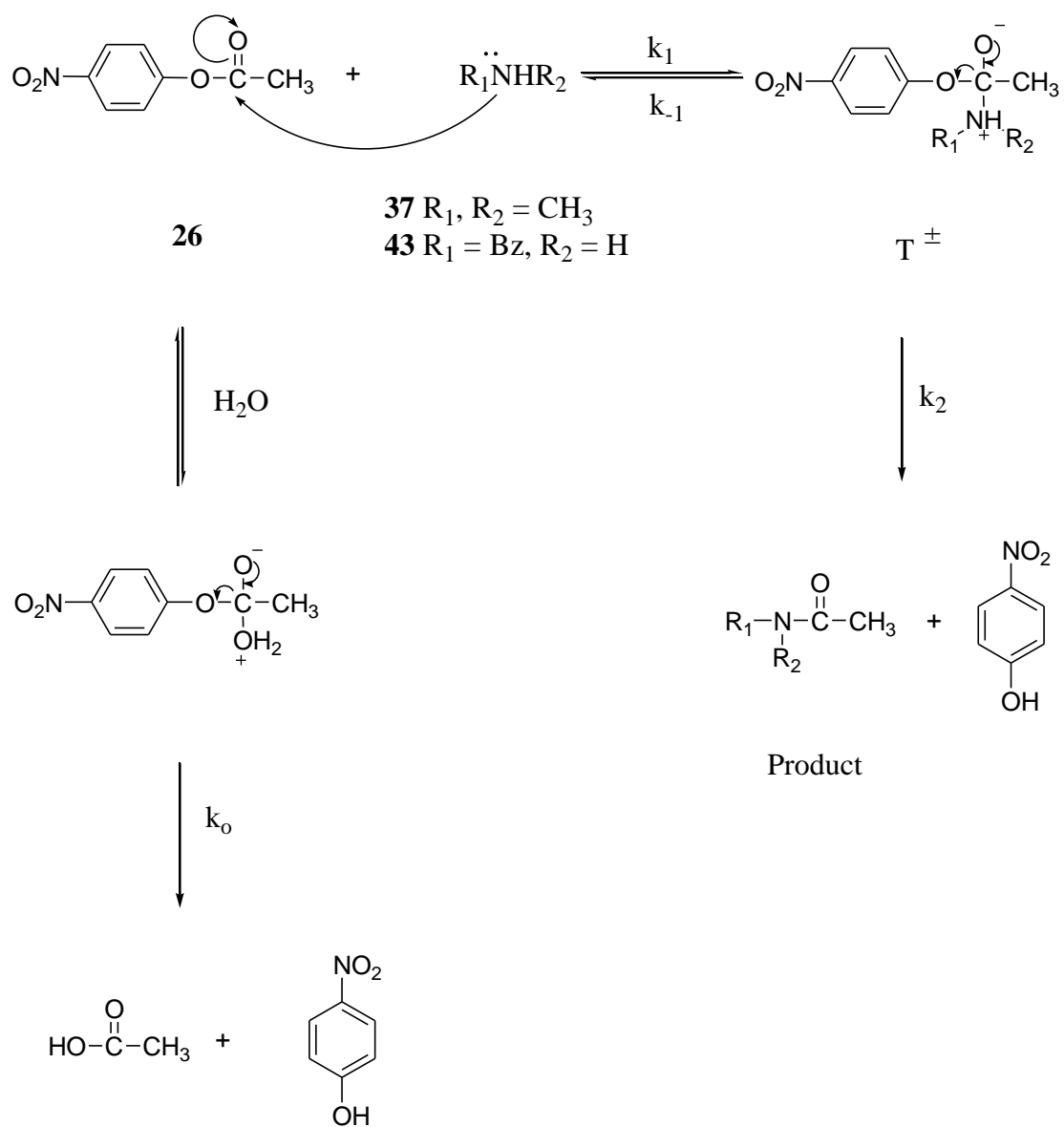
4.4.1 Primary and Secondary Amines

The plots of k_{obs} versus total amine buffer $[\text{Buf}]_{\text{T}}$ gave straight line. The rate law is expressed as Eq. (3-14), where $[\text{Sub}]_{\text{T}}$ = total concentration of **26**. The Eq. (3-14) gave Eq. (3-15) where, k_{o} = neutral hydrolysis, k_{b} = second-order rate constant and $[\text{Am}]$ = primary and secondary amines. In most cases, the plots gave almost zero intercept, which indicates that the neutral hydrolysis, k_{o} of the ester was insignificant in all cases. The straight line graph also indicates that there were no occurrences of general acid-general base (GA-GB) catalysis in the aminolysis of **26** by primary and secondary amines. The slope represents k_{b} , (second-order rate constant nucleophilic aminolysis of **26**). The same result was reported by Ik-Hwan et al. for aminolysis of *o*-4-nitrophenyl thiobenzoate with primary amine but exhibits an upward curvature for secondary amines.²⁶ There are reports that show that, the aminolysis of phenyl esters by primary and secondary amines involves both general base and general acid catalyzed nucleophilic attack of amine at the carbon carbonyl of ester.^{6,18,19,21} Gold et al. from their study, made a conclusion that, the better leaving group (i.e. the lower the pK_{a} of the phenol) the greater the tendency for nucleophilic catalysis to occur.³¹

The plots of A_1 versus $[\text{OH}^-]$ for primary and secondary amines are generally linear. This observation indicates that, there were no occurrences of other catalyzed terms such as general acid - general base (GA-GB) catalyzed except the nucleophilic catalyzed terms. For the *N,N*-diethylamine, the plot gave negative slope which indicated k_{OH^-} as meaningless (absent of specific base catalysis). This may be attributed to the presence of steric effect. The values of k_{n} range from 0.0178 to 6.78 M^{-1}

$^1\text{s}^{-1}$ for methylamine and benzylamine respectively. The values of k_n range from 0.00136 to $2.90 \text{ M}^{-1}\text{s}^{-1}$ for secondary amines. The values of k_n was controlled by the steric effect. The more group attached to the nitrogen, the crowded it becomes and as a consequence nitrogen becomes a weaker nucleophile. The similar explanations may be made for the values of k_{OH^-} .

The detailed mechanism for the nucleophilic cleavage of **26** in buffers of primary and secondary amines may be expressed by Scheme 4-2. Amines attack at carbonyl carbon to form zwitterionic tetrahedral intermediate, T^\pm . The intermediates T^\pm are so unstable in aqueous solution that they cannot be directly detected by any usual spectral technique.⁶ The expulsion of the leaving group from zwitterionic tetrahedral addition intermediate becomes the rate - determining step in the nucleophilic reaction of primary, secondary and tertiary amines with phenyl and *p*-nitrophenyl acetate as evident from the Bronsted plot, $\beta = 0.9$.^{6,19} There is no change in rate - determining step for the reaction of phenyl acetate (with a pK_a of leaving group = 10) with amines of pK_a as low as 3.5.²³ The aminolysis of **26** depend on the relative basicity of the nucleophile and basicity (pK_a) of leaving group. The rate increases as the basicity of the amine increases, but decreases as the steric bulk of the alkyl group increases. Thus, the decreases of k_b values are expected due to the increased of alkyl groups. For a leaving group of pK_a lower than that of the nucleophiles, the nucleophilic attack is the rate determining - step. The evidence through product characterization was discussed in previous chapter 3. The plots of A_1 versus $[\text{OH}^-]$ for primary and secondary amines gave straight lines with slope = k_n and intercept = k_{OH^-}



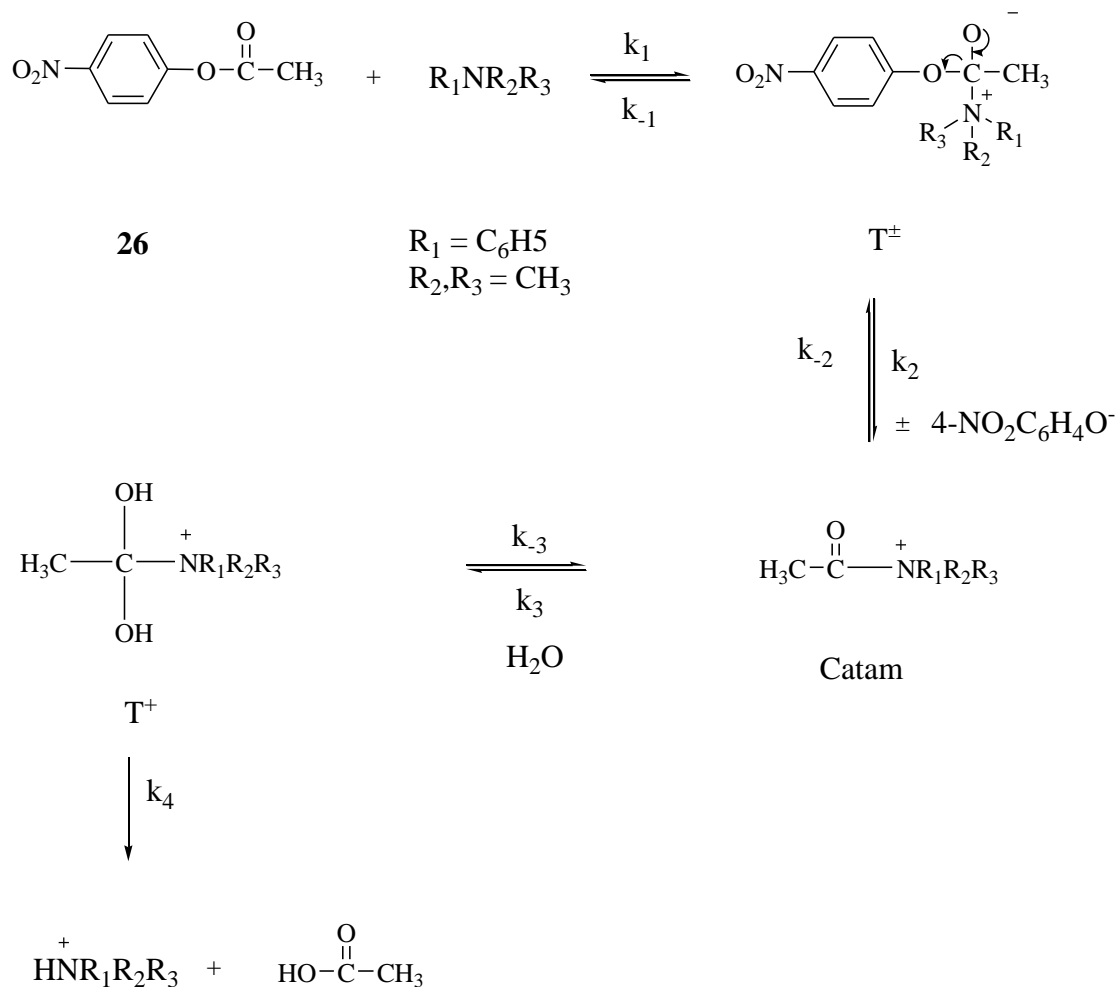
Scheme 4-2

4.4.2 Tertiary Amines

The plots of k_{obs} versus total buffer $[\text{Buf}]_{\text{T}}$ gave straight lines. The rate of hydrolysis of **26** showed no clear increase with the increasing total buffer concentration. The observed rate law is expressed as Eq. (3-14). The Eq. (3-14) gave Eq. (3-15) where, k_0 = neutral hydrolysis, k_b = second-order rate constant and $[\text{Am}]$ = tertiary amines.

The plots gave almost zero intercept, which indicated that the neutral hydrolysis, k_o of the ester was insignificant in all cases. The straight line graph indicates the absence of general acid catalysis in the aminolysis of **26** by tertiary amines. The slope represents k_b (second-order rate constant of hydrolysis of **26**). The values of k_b revealed no clear increase in the rate constant with the increasing buffer concentrations. The rate constant $k_n = (3.37 \pm 0.40) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ for the cleavage of **26** by **53** may be compared with reported values $k_n = < 1 \times 10^{-3}$ (in aqueous solution, $\mu = 1.0 \text{ M}$).³²

The detailed mechanism for the hydrolysis of **26** by buffered tertiary amines solution may be expressed by Scheme 4-3. The reaction of tertiary amine with ester must be *via* simple nucleophilic attack at the ester carbonyl group. Most of the aliphatic tertiary amines are strong bases ($\text{pK}_a \geq 10$), and that is why these amines, although sterically hindered, act as efficient nucleophile.⁶ The value of pK_a of **53** is 9.03, it is a good nucleophile. The reported values of k_b for different tertiary amines yields a Bronsted plot of slope (β) of 0.70 and intercept (c) of $8.45 \text{ M}^{-1}\text{sec}^{-1}$.^{6,32} The intermediates T^\ddagger and T^+ are so unstable in aqueous solution that they cannot be directly detected by any usual spectral technique. In the cleavage of **26**, under amines with $\text{pK}_a < 11$, the expulsion of the leaving group from zwitterionic tetrahedral addition intermediate as the rate determining step. The evidence through product characterization was discussed in previous chapter 3. The plot of A_1 versus a_{OH} for **53** gave straight line with slope = k_n and intercept = k_{OH} , obeyed Eq. (4-5).



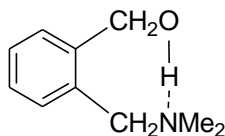
Scheme 4-3

4.4.3 Amino Alcohol

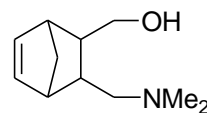
The plots of k_{obs} versus total buffer concentration, $[\text{Buf}]_{\text{T}}$ for aminolysis of **26** by amino alcohol gave straight line. The rate of hydrolysis of **26** by amino alcohol showed no clear increase in rate with the increasing buffer concentration. The observed rate law is expressed as Eq. (3-14). The Eq. (3-14) gave Eq. (3-15) where, k_0 = neutral hydrolysis, k_b = second-order rate constant and $[\text{Am}]$ = amino alcohol.

The plots of k_{obs} versus $[\text{Buf}]_{\text{T}}$ produced linear plots of almost zero intercept, which indicate that the neutral hydrolysis, k_0 , was insignificant in all cases. The straight line graph indicates the absence of general acid - general base (GA-GB)

catalysis in the aminolysis of **26**. The study, using *o*-(*N,N*-dimethylamino)benzyl alcohol (**32**) as a buffer, reveals the presence of intramolecular induced nucleophilic catalyst in the cleavage of **26**.^{32,33} The compound shows extensive internal hydrogen bonding in aqueous solvent (**54**), and this characteristic makes the hydroxyl group more effective nucleophile compared with nitrogen nucleophile. Similar observation was showed by compound 2-endo-[(dimethylamino)methyl]-3-endo-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**55**). Werber and Shalitin showed similar observation for the reaction of amino alcohols with **26**. The formations of product of *o*-acyl-amino alcohol is due to the presence of internal hydrogen bond.³⁶



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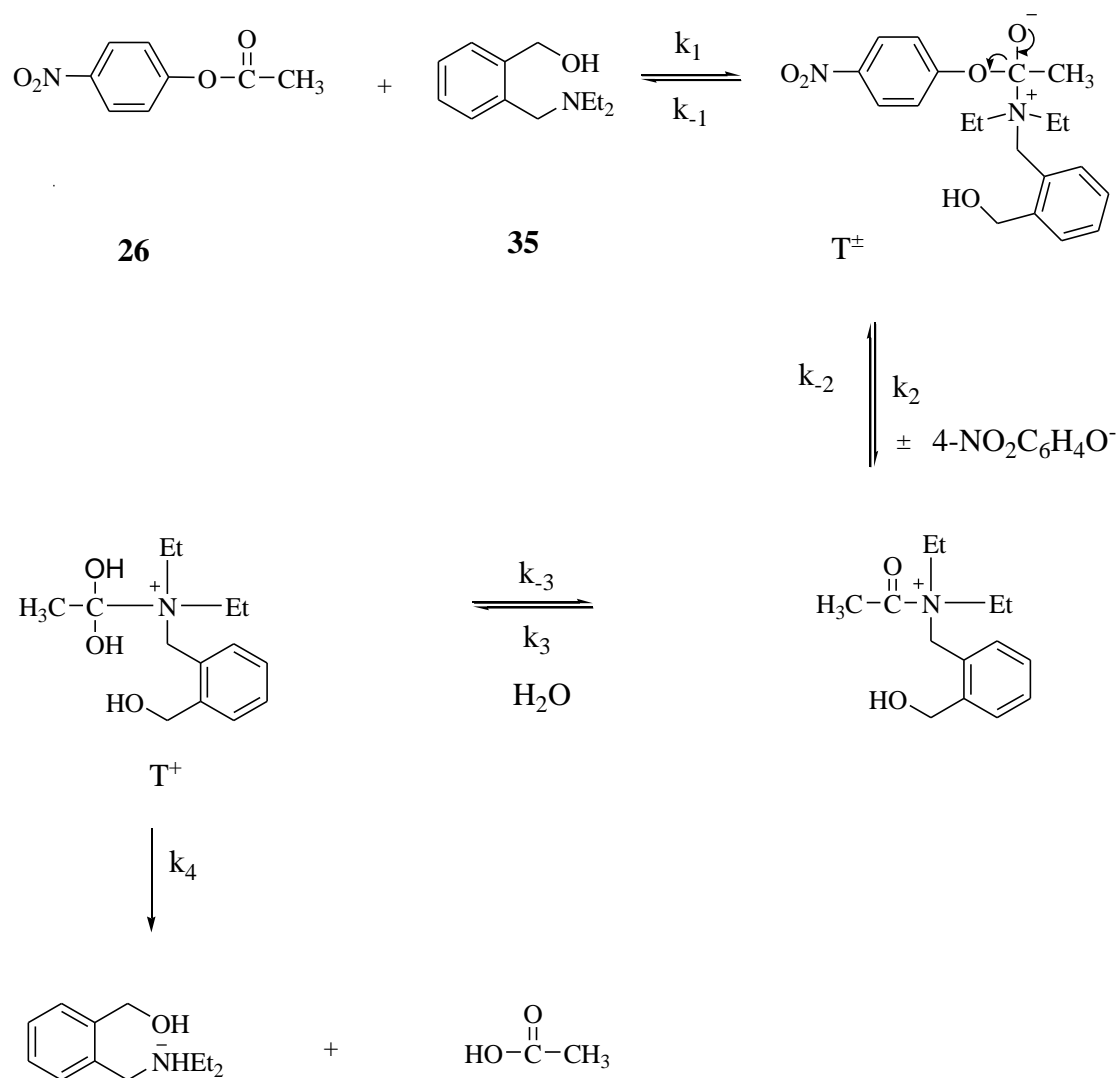


55

The compound **35** which, differs in term of substituent attached to amine nitrogen gave negative result for intramolecular induced nucleophilic catalyst. Even the values of k_{obs} for the cleavage of **26** by **35** show higher values than the values of k_{obs} for the cleavage of **26** by **53**. There was no internal hydrogen bonding in compound **35**. This makes the nitrogen acts as better nucleophile than oxygen nucleophile. The hydrolysis of **26** by compound **35** gave **48** and **31** as final products without the formation of ester as intermediate product as evidenced show in HPLC results discussed in Chapter 3.

The rate constant of nucleophilic catalysis, $k_n = (4.40 \pm 0.30) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ for **35** is larger than k_n for *N,N*-dimethylbenzylamine $(3.37 \pm 0.40) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$. These due to presence and absence of hydroxyl (OH) group in **35** and **43**, respectively. The

detailed mechanism for the hydrolysis of **26** in buffered amino alcohol solutions may be expressed by Scheme 4-4. Amines act as nucleophile to form zwitterionic tetrahedral intermediate, T^\pm .



Scheme 4-4

4.4.4 Bronsted Plot

Nucleophilic second - order rate constant, k_n , obtained for aminolysis of **26** in the presence of primary and secondary amines has been found to follow the Bronsted equation (4-8)

$$\log k_n = C + \beta_{\text{nuc}} \text{pK}_a \quad (4-8)$$

A Bronsted plot of $\log k_n$ versus pK_a is shown graphically in Fig. 4-17. A straight line passing through 6 points of amines covering the pK_a values ranging from 8.86 – 10.56 results in slope (β_{nuc}) of 0.91 ± 0.20 and intercept (C) $-9.12 \pm 1.9 \text{ M}^{-1}\text{s}^{-1}$. The fitting of the observed data to Eq. (4-8) is evident from the plot shown in Fig. 4-17 where the solid line is drawn through the least-squares calculated data points. The values of pK_a , k_n and k_{nald} are summarized in Table 4-20. For reaction of the primary and secondary amines with **26**, a linear Bronsted correlation was observed between the rate constant and amines basicity. This plot was not included *N,N*-dimethylamine and **35** because these amines are the members of a different series.

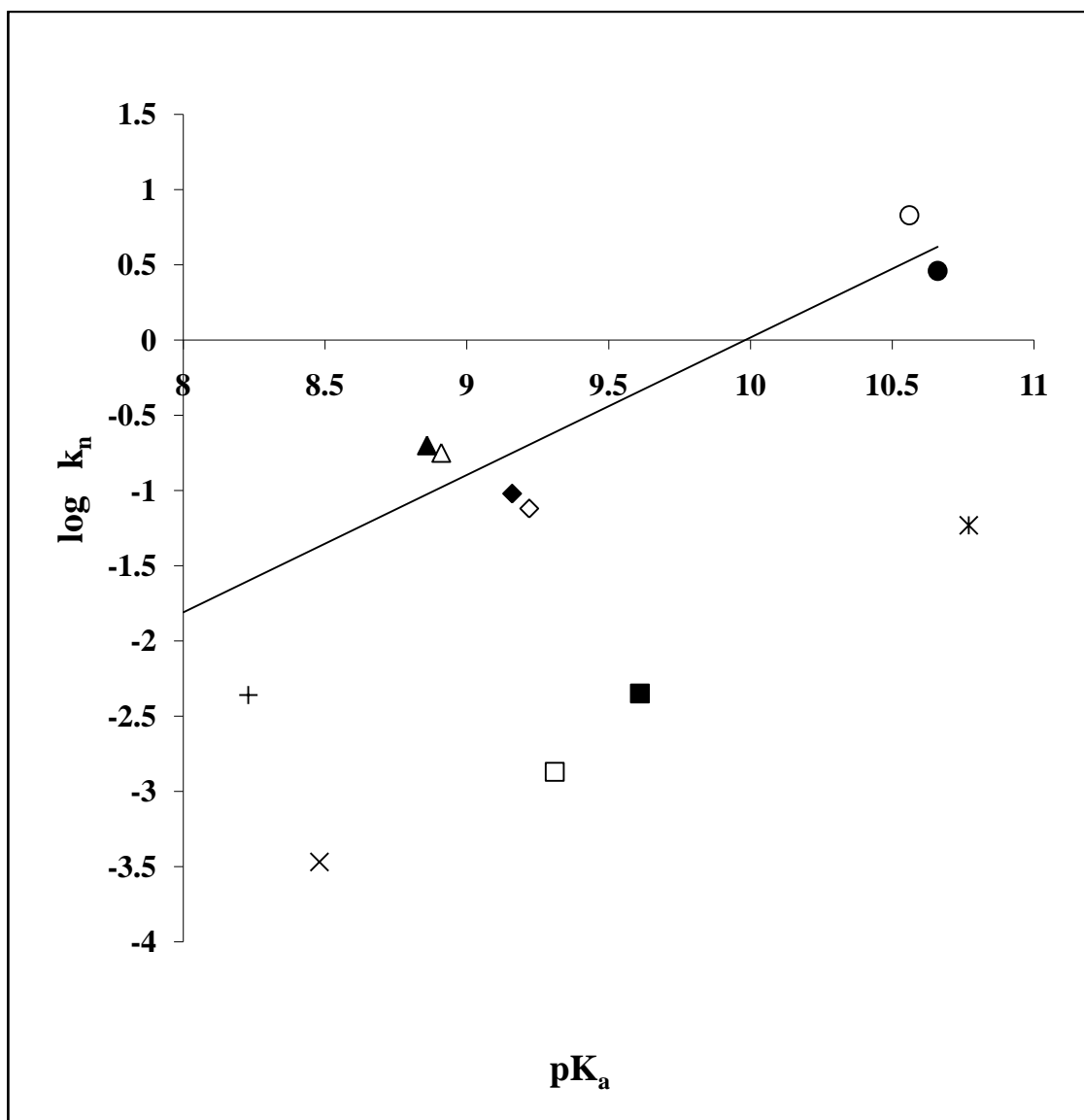


Figure 4-17 : The dependence of the nucleophilic second-order rate constant (k_n) for the reaction of **26** with amines nucleophiles on the pK_a of the conjugate acid of the amines at 30°C. The solid line is drawn through the least-squares calculated points using Bronsted equation with slope (β_{nuc}) of 0.91 ± 0.20 and intercept (C) $-9.12 \pm 1.8 \text{ M}^{-1}\text{s}^{-1}$. In the Bronsted plot : Methylamine (\circ)^a, *N*-benzylamine (Δ), *N*-benzylamine (\blacktriangle)^b, *N,N*-dimethylamine (\bullet)^a, *N,N*-diethylamine ($*$)^a, *N,N*-methylbenzylamine (\diamond)^a, *N,N*-methylbenzylamine (\blacklozenge)^b, *N,N*-ethylbenzylamine (\square)^a, *N,N*-ethylbenzylamine (\blacksquare)^b, *N,N*-dimethylbenzylamine (\times)^a and *N,N*-(diethylaminomethyl)benzyl alcohol ($+$)^a.

^a $\mu = 0.4 \text{ M}$

^b $\mu = 0.3 \text{ M}$

Table 4-20: Values of pK_a , k_n , and k_{ncald} – Bronsted plot of Aminolysis of **26** by Amines.

Amines	pK_a ^a	k_n ($M^{-1}s^{-1}$)	$\log k_n$ ($M^{-1}s^{-1}$)	$\log k_{ncald}$ ($M^{-1}s^{-1}$)
Methylamine (○) ^b	10.56	6.78 ± 0.2 ^{c,d}	0.83	0.53
<i>N</i> -Benzylamine (Δ) ^b	8.91	$(17.8 \pm 1.4) \times 10^{-2}$ ^{c,d}	-0.75	-0.98
<i>N</i> -Benzylamine (▲) ^e	8.86	$(19.9 \pm 1.3) \times 10^{-2}$ ^{c,d}	-0.70	-1.02
<i>N,N</i> -Dimethylamine (●) ^b	10.66	2.90 ± 3.4 ^{c,d}	0.46	0.62
<i>N,N</i> -Diethylamine (*) ^b	10.77	$(59.3 \pm 4.8) \times 10^{-3}$ ^f	-	-
<i>N,N</i> -Methylbenzylamine (◇) ^b	9.22	$(7.53 \pm 1.1) \times 10^{-2}$ ^{c,d}	-1.12	0.70
<i>N,N</i> -Methylbenzylamine (◆) ^e	9.16	$(9.61 \pm 0.8) \times 10^{-2}$ ^{c,d}	-1.02	-0.75
<i>N,N</i> -Ethylbenzylamine (□) ^b	9.31	$(1.36 \pm 0.84) \times 10^{-3}$ ^f	-	-
<i>N,N</i> -Ethylbenzylamine (■) ^e	9.61	$(4.48 \pm 0.60) \times 10^{-3}$ ^f	-	-
<i>N,N</i> -Dimethylbenzylamine (×) ^b	8.48	$(3.37 \pm 0.40) \times 10^{-4}$ ^f	-	-
<i>N,N</i> -(Diethylaminomethyl)benzyl alcohol (+) ^b	8.23	$(4.40 \pm 0.30) \times 10^{-3}$ ^f	-	-

^a $pK_a = pH_{av}$ at 50 % free base in this study.

^b $\mu = 0.4$ M

^c Error limits are standard deviations.

^d Calculated from Eq. (4-8).

^e $\mu = 0.3$ M

^f Data are not included in determine the β_{nuc} value.

Linear free-energy relationships, such as Bronsted – type equation, has been most commonly used to determine reaction mechanism. The changes in the value of β_{nuc} have a significant meaning. A small value of β_{nuc} indicates that the nucleophilic attack is rate – determining step while the large vale of β_{nuc} indicates the expulsion of the leaving group as the rate – determining step. The value of β_{nuc} of 0.8 for the reaction of nucleophilic reagent with phenyl acetate indicates a large sensitivity of the reaction to the basicity of nucleophiles. The value of $\beta_{nuc} = 0.91 \pm 0.20$ is in aggrement with the value of $\beta_{nuc} 0.9 \pm 0.1$ for the aminolysis of substituted phenyl acetate and AMPP by various primary, secondary and tertiary amines.¹⁹

The value of β_{nuc} was consistent with the rate – determining breakdown of T^\ddagger , in which nitrogen bears nearly fully positive charge in the transition state.²⁷ The value of β_{nuc} of 0.9 is attributed to the expulsion of the leaving group (aryl ions, ArO^-) from the zwitterionic tetrahedral intermediate as the rate-determining step in the nucleophilic reaction of primary, secondary and tertiary amines with *p*-nitrophenylacetate as well as phenyl acetate.^{6,19}

Methylamine (pKa 10.56) and *N,N*-dimethylamine (pKa = 10.66) fall very close to the linear plot. *N,N*-Diethylamine (pKa = 10.77) fall far from the linear plot, but this not meant that the aminolysis of **26** by *N,N*-diethylamine occurred through different path. Reported values Bronsted slope and intercepts for hydrolysis of **26** by various tertiary amino alcohol and tertiary amines are $\beta = 0.89$, $C = -8.49$ ³⁷ and $\beta = 0.70$, $C = 0.26$, respectively.^{32,34}

Third – order rate constant for specific base – catalyzed aminolysis of **26** in the presence of primary and secondary amines has been found to follow the Bronsted equation (4-9)

$$\log k_{\text{OH}'} = C + \beta_{\text{nuc}} \text{pK}_a \quad (4-9)$$

A Bronsted plot of $\log k_{\text{OH}'}$ versus pK_a is shown graphically in Fig. 4-18. A straight line passing through 6 points of amines covering the pK_a values ranging from 8.86 – 10.56 results in slope (β_{nuc}) of 0.88 ± 0.20 and intercept (C) $-5.40 \pm 1.9 \text{ M}^{-1}\text{s}^{-1}$. The fitting of the observed data to Eq. (4-9) is evident from the plot shown in Fig. 4-18 where the solid line is drawn through the least-squares calculated data points. The values of pK_a , $k_{\text{OH}'}$ and $k_{\text{OH}'\text{cald}}$ are summarized in Table 4-21. The point for *N,N*-Ethylbenzylamine falls far to the linear plot, this may be explained due to the steric

effect. The plot turned to be similar with the plot of $\log k_n$ versus pK_a . This shows an agreement with the observed result for second – order rate constant, k_n .

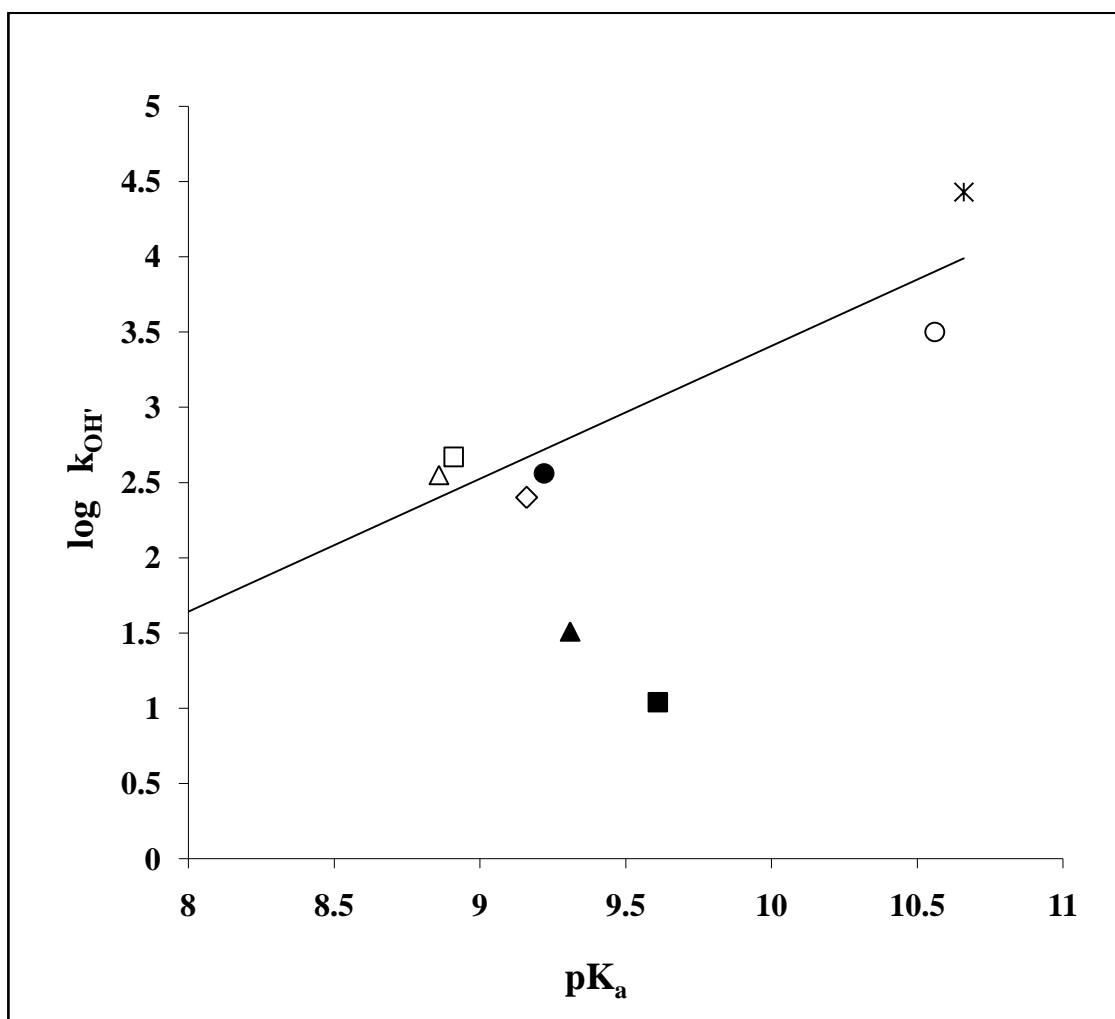


Figure 4-17 : The dependence of the third - order rate constant (k_{OH^-}) for the reaction of **26** with amines nucleophiles on the pK_a of the conjugate acid of the amines at 30°C. The solid line is drawn through the least-squares calculated points using Bronsted equation with slope (β_{nuc}) of 0.88 ± 0.20 and intercept (C) $-5.40 \pm 1.9 M^{-1}s^{-1}$. In the Bronsted plot : Methylamine (○)^a, *N*-benzylamine (□), *N*-benzylamine (Δ)^b, *N,N*-dimethylamine (*)^a, *N,N*-methylbenzylamine (●)^a, *N,N*-methylbenzylamine (◇)^b, *N,N*-ethylbenzylamine (▲)^a, *N,N*-ethylbenzylamine (■)^a. $\mu = 0.4 M$,^b $\mu = 0.3 M$

Table 4-21: Values of pK_a , $k_{OH'}$, and $k_{OH'cald}$ – Bronsted plot of specific base – catalyzed aminolysis of **26**.

Amines	μ	pK_a^a	$k_{OH'}$ ($M^{-2}s^{-1}$)	\log $k_{OH'}$	\log $k_{OH'cald}$
Methylamine (\circ)	0.4	10.56	$3179 \pm 866^{b,c}$	3.50	3.90
<i>N</i> -Benzylamine (\square)	0.4	8.91	$465 \pm 125^{b,c}$	2.67	2.44
<i>N</i> -Benzylamine (Δ)	0.3	8.86	$358 \pm 111^{b,c}$	2.55	2.41
<i>N,N</i> -Dimethylamine (*)	0.4	10.66	$26693 \pm 13107^{b,c}$	4.43	3.99
<i>N,N</i> -Diethylamine	0.4	10.77	- ^d	-	-
<i>N,N</i> -Methylbenzylamine (\bullet)	0.4	9.22	$365 \pm 74^{b,c}$	2.56	2.72
<i>N,N</i> -Methylbenzylamine (\diamond)	0.3	9.16	$253 \pm 61^{b,c}$	2.40	2.66
<i>N,N</i> -Ethylbenzylamine (\blacktriangle)	0.4	9.31	32 ± 6^d	1.51	-
<i>N,N</i> -Ethylbenzylamine (\blacksquare)	0.3	9.61	11 ± 4^d	1.04	-

^a $pK_a = pH_{av}$ at 50 % free base in this study.

^b Calculated from Eq. (4-9).

^c Error limits are standard deviations.

^d Data are not included in determine the β_{nuc} value.

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CONCLUSIONS

Aminolysis of **26** with primary and secondary amines does not reveal the occurrence of general acid – general base (GA – GB) catalysis. These amines does show the presence of specific base catalysis (k_{OH^-}) and exception to it is found with *N,N*-diethylamine and other tertiary amines. The cleavage of **26** under buffers of primary and secondary amines gave amides and phenolate ion as final products. Meanwhile, the cleavage of **26** with tertiary amine reveals the presence of nucleophilic catalysis. It is exhibited by linear plot of k_{obs} versus total amine buffer ($[\text{Buf}]_{\text{T}}$).

The cleavage of **26** under the buffers of tertiary amino alcohol shows the presence of nucleophilic catalysis as evidenced by the linear plots of k_{obs} versus total amine buffer ($[\text{Buf}]_{\text{T}}$). The nucleophilic second – order rate constant (k_{n}) value of amino alcohol is higher than k_{n} value of tertiary amine. The kinetic data reveal the absence of internal hydrogen bonding between hydroxyl and tertiary amino group.

The reaction mechanism of aminolysis of **26** involves the direct attack of nitrogen nucleophile at carbonyl carbon to form zwitterionic tetrahedral intermediate, T^{\pm} , where the expulsion of leaving group is the rate – determining step. This was in agreement with the value of Bronsted plot, (β_{nuc}). The buffered – catalyzed cleavage of **26** under the buffers of primary and secondary amines revealed a Bronsted plot of slope (β_{nuc}) of 0.91 ± 0.20 and intercept (C) $-9.12 \pm 1.9 \text{ M}^{-1}\text{s}^{-1}$.

